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AMYLOID DEGENERATION OF THE ADRENALS AS A FACTOR IN PRODUCING SYMPTOMS OF ADDISON'S DISEASE IN CHRONIC PULMONARY TUBERCULOSIS[1, 2]

I. D. BRONFIN[3] AND PAUL H. GUTTMAN

Considering that tuberculosis of the adrenals is responsible for about 70 per cent of cases of Addison's Disease, it is difficult to explain the unusually low incidence of this disease in tuberculosis sanatoria. Minor (1) did not observe a single case in a period of 35 years, while Brown (2) records 3 cases in 2,570 deaths of former patients at Trudeau Sanatorium.

Until relatively recently our experience has been similar. In a period of 15 years of exclusive sanatorium practice we have encountered only 2 cases of Addison's Disease due to bilateral adrenal tuberculosis in approximately 4,500 patients. To explain the low-reported incidence in sanatoria of Addison's Disease due to tuberculosis of the adrenals, a number of factors must be considered. Extensive bilateral fibrocaseous tuberculosis of the adrenals is usually seen in cases with minimal or healed primary tuberculosis of the lung, and only rarely in extensive bilateral pulmonary tuberculosis. Extensive disease of the adrenals often develops long after the patient has been dismissed from a sanatorium as an arrested case and, therefore, does not come under observation in sanatoria. Moreover, in extensive pulmonary tuberculosis, symptoms of adrenal insufficiency may be obscured by symptoms of the primary lesions which may simulate closely those of Addison's Disease.

Notwithstanding the rarity of frank Addison's Disease in tuberculosis institutions, the dissimilarity of clinical manifestations in many ultimately fatal cases of pulmonary tuberculosis has led us to suspect adrenal insufficiency as a factor in those patients whose asthenia, loss of weight, anorexia and abdominal distress were out of proportion to the

[1] From the Medical Department, National Jewish Hospital, Denver, Colorado, and the Department of Pathology, University of Colorado School of Medicine, Denver.

[2] Presented before the Pathological Section at the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 16, 1934.

[3] It is with sincere regret that the REVIEW records the death of Dr. Bronfin which occurred after this paper was submitted but prior to its final publication.

extent or activity of the pulmonary lesions. The first case of this type (case 1, group 1) came under our observation in May, 1927. The asthenia was markedly out of proportion to the pulmonary lesion and the sallow appearance of the skin with pigmentation over the forehead, nose and sides of the neck attracted our attention to the possibility of associated Addison's Disease. The absence of pigmentation of the buccal mucous membrane did not exclude the possibility of Addison's Disease, for it was recalled that in Lewin's (3) series there were 64 proved cases without any pigmentation. In the past few years we observed a number of such cases, and the symptoms, notably the asthenia and gastrointestinal disturbances, led us to suspect that the underlying factor was adrenal insufficiency due to bilateral amyloid infiltration of the adrenals.

This report is based upon a study of 14 patients who showed varying degrees of amyloid degeneration of the adrenals. The clinical evaluation of the symptoms was made independently of the pathological study; the two were correlated subsequently. These cases were classified clinically into 3 groups. In the first or positive group were included those patients whose symptoms appeared quite characteristic of Addison's Disease and who, in addition, presented some degree of pigmentation. In the second or questionable group were included those cases with borderline symptoms which, because of the associated extensive pulmonary tuberculosis or tuberculosis elsewhere in the body, could not be properly evaluated from the standpoint of Addison's Disease. The third or negative group was compiled only after this investigation was undertaken.

Amyloid infiltration of the adrenals is found in a large proportion of cases in association with amyloid infiltration of the spleen, liver, kidneys and other organs. Blum (4), in 1903, found the adrenals involved in only one of 221 cases of amyloid disease. However, he admitted that this low incidence was due to the fact that the adrenals were not examined routinely. Lubarsch (5) found amyloid in the adrenals in 95 per cent of the cases of generalized amyloidosis as compared to 97 per cent involvement of the spleen and 82 per cent of the kidneys. Wicht (6) states that 97 per cent of his cases showed involvement of the adrenals in generalized amyloidosis. In the present series of 100 tuberculosis cases, 18 cases of amyloid disease were found. Of these, 14, or 78 per cent, showed amyloid infiltration of the adrenals.

Although the amount of amyloid deposits is subject to considerable variation in different organs of the same individual, one usually finds

that in cases of marked generalized amyloidosis the adrenals show extensive deposits of amyloid substance. On the other hand, there are many known instances in which amyloid deposits may be extensive in one organ and absent in other organs. In the present study, one case showed extensive amyloid deposits in the spleen, whereas no amyloid was seen in the liver, kidneys or adrenals. Primary amyloidosis of the adrenals is extremely rare.

The frequency of Addison's Disease resulting from amyloid involvement is extremely low as compared to Addison's Disease due to bilateral tuberculosis of the adrenals. Guttman (7), in an analysis of 566 cases of Addison's Disease contained in the literature from 1900 to 1930, inclusive, found only 7 cases, or 1.73 per cent, in which amyloid infiltration of the adrenals occurred. These cases were reported by Bittorf (8), Hunter and Rush (9), Schultz (10), Schlesinger (11), Bauer (12), McCutcheon (13) and Philpott (14). It is doubtful that Bauer's case is truly Addison's Disease. The amyloid disease was associated with chronic pulmonary tuberculosis in only 2 cases (Hunter and Rush, Philpott). The others showed the following underlying causes for amyloid disease: syphilis, 2 cases; hypernephroma, 1 case; chronic nephritis, 1 case.

To explain the extreme rarity of case-reports of Addison's Disease due to amyloid infiltration of the adrenals, 3 possibilities are suggested: First, that sufficient cortical tissue is preserved to prevent symptoms of the disease; second, that the medulla, which is spared in amyloid infiltration, prevents the development of Addison's Disease; and, third, that symptoms of Addison's Disease may be masked in many cases by the underlying pathological condition, usually a widespread chronic pulmonary tuberculosis.

It is true that even in very extensive amyloid involvement of the adrenals, small islands of cortical tissue and the outer portion of the zona glomerulosa are entirely free of amyloid deposit and appear normal histologically. While these uninvolved areas of cortical cells in all probability play an important rôle in preventing symptoms of Addison's Disease in many cases, it is difficult to determine what proportions of the cells are unaffected and the degree of functional impairment of the atrophied cortical cells. From a study of the severe examples of amyloid infiltration of the adrenals in this series, it appears that destruction is as extensive as one finds in bilateral tuberculosis of the adrenals and atrophy associated with Addison's Disease. In cases of adrenal atrophy large

areas of well-preserved cortical cells may be seen, and, in addition, small circumscribed newly formed cortical adenoma may also be found.

Although the medulla is comparatively unharmed in amyloid infiltration of the adrenals, it is highly questionable that this portion plays an important rôle in the production of symptoms of Addison's Disease. Wiesel's (15) view that the chromaffin system is partly responsible for symptoms of Addison's Disease has not held up against experimental investigation and the clinical-pathological investigation of Karakascheff (16), Fahr and Reiche (17), and others. Addison's Disease is seen in its complete clinical manifestations in association with atrophy (primary contracted adrenals), in which medullary tissue is not harmed, the destruction of the cortex constituting the primary lesion.

Since Addison's Disease is generally considered in 3 phases, namely, the latent phase, when there are few or no symptoms, the phase in which the disease is usually recognized and consists of the classical picture described by Addison, and the final phase of collapse associated with extreme nausea, vomiting, dehydration and cardiac failure, it is obvious that, in this group of patients who were suffering from progressive pulmonary tuberculosis with complications, the first phase and even the second phase could not always be detected unless pigmentation was present. It was the third phase in the majority of instances that gave a clue to the possibility that the syndrome might be due rather to adrenal insufficiency than to the primary disease. Although the symptoms in many of these cases were similar, there were salient features in each case warranting a detailed description of the entire group in accordance with their respective classification.

GROUP 1

Patients Showing Characteristic Symptoms of Addison's Disease

Case 1: E. S., no. 5,850. Female, age 30. Admitted August 22, 1925, with history of pulmonary tuberculosis of 3 years' duration. The pulmonary lesion was far advanced, bilateral, and with cavitation in both apices. The clinical course was characterized by subfebrile temperature, progressive weakness and loss of weight. When first seen by one of us in May, 1927, the attention was attracted to the sallow appearance of the skin with pronounced pigmentation of the forehead, nose and neck. The patient had not been exposed to the sun and was certain that the "freckles" made their appearance during her residence in the sanatorium. Her principal complaints at this time were anorexia, abdominal cramps and diarrhoea and frequent fainting attacks with temporary

loss of consciousness. There were premonitory symptoms of such attacks and she was able to avert them by the use of aromatic spirits of ammonia. The blood-pressure in November, 1927, was 130/100 and in October, 1928, 120/90. The urine showed 2- to 4-plus albumin and the blood showed evidence of a secondary anaemia. Sudden circulatory collapse with distressing gastro-intestinal symptoms became manifest several days before death, which occurred on November 15, 1928.

Anatomical diagnosis: Fibroid tuberculosis of lungs with cavity-formation; miliary tubercles of heart-muscle, kidney, liver and spleen; moderate arterio-sclerosis; amyloid disease of spleen, liver, kidneys and adrenals and mild tuberculous colitis.

Gross pathology: A large, well walled-off cavity occupies the apex of the left lung. Below this are numerous nodular caseous areas and recent tuberculous pneumonia of the lower lobe. There is a marked thickening of the pleura. The right lung contains a well encapsulated cavity at the apex and a fairly fresh cavity in the lower lobe. Foci of tuberculous bronchopneumonia occupy the middle and lower lobes. Several small shallow tuberculous ulcers are present in the caecum. The liver, spleen and kidneys are enlarged and unusually firm. *The adrenals are normal in size and appearance.*

Microscopic changes of adrenals:[4] Both the zona fasiculata (*Z. F.*) and zona reticularis (*Z. R.*) are extensively infiltrated with large masses of amyloid. There are atrophy and necrosis of most of the epithelial structures in these zones. The zona glomerulosa (*Z. G.*) is involved to a lesser extent. Fairly well-preserved clusters of cortical cells are seen in the outer *Z. G.* The medullary tissue is well preserved. Islands of cortical cells lying about the central veins are markedly infiltrated with amyloid.

Case 2: A. G., no. 6,197. Male, age 34. Admitted March 26, 1927, with a history of pulmonary tuberculosis of 6 years' duration. Physical and X-ray examinations disclosed far-advanced, bilateral, fibroid pulmonary tuberculosis involving both upper lobes with cavitation. The laryngoscopic examination showed a distorted but well-scarred epiglottis and fibrosed cords. The skin was somewhat brownish in color, which the patient attributed to heliotherapy. The urine showed consistently 2- to 3-plus albumin and white blood cells. The pulmonary lesion was only slowly progressive. Asthenia was the principal clinical feature. The weakness at times was so pronounced that talking or lifting a hand or arm seemed too much of an effort. Dyspnoea was quite pronounced after the slightest exertion. During the last 9 months of residence, pigmentation became manifest over the frontal eminences extending on each

[4] A detailed description of the relation of the amyloid deposits to the reticulum, sinuses and epithelial cells will be given following the case-reports. In this case-report and the following ones, a description of the extent of the amyloid deposits is given.

side down towards the ears and neck. There was no pigmentation of the buccal mucus membrane. The blood-pressure in October, 1928, was 80/65, with averages of 70/50. The terminal manifestations, in addition to progressive weakness, were anorexia, abdominal cramps and diarrhoea, nausea and vomiting, with loss in weight of 12 pounds in three months. Death occurred rather suddenly on November 16, 1930, during a fainting attack to which the patient had been subject for quite some time.

Anatomical diagnosis: Chronic pulmonary tuberculosis, with cavitation, bilateral; encapsulated empyema, right pleural cavity; tuberculosis of larynx and trachea; tuberculous pyonephrosis of right kidney; tuberculosis of bladder, prostate, epididymis; miliary tubercles of spleen; tuberculous enterocolitis; amyloid infiltration of liver, spleen, stomach, kidneys and adrenals.

Gross pathology: The body is poorly nourished. The skin has a brownish tinge. A small encapsulated abscess is present in the pleura between the anterior margins of the right lower lobe and diaphragm. A large thick-walled cavity occupies the right upper lobe. The middle lobe is honeycombed with small cavities. The lower lobe shows scattered firm nodules. The left upper lobe contains a large cavity near the apex. The lower lobe contains numerous small cavities and firm caseous nodules. The larynx shows numerous white nodules beneath the epithelium and areas of ulceration. The spleen is markedly enlarged and firm. The cut-surface is mottled with numerous dark translucent spots giving the appearance of a typical "sago" spleen. Several small ulcers are noted in the mucosa of the ileum near the ileocaecal valve. The liver is moderately enlarged. The cut-surface is pale and mottled and the substance firm. The right kidney shows a small abscess in the lower pole. The pelvis of the kidney is dilated and contains a thick purulent fluid. The bladder shows a hyperaemic granular surface about the trigone. The prostate shows 3 to 4 small caseous nodules.

Microscopic examination of adrenals: There are extensive amyloid deposits occupying for the most part the *Z. F.* The *Z. R.* in places shows absence of amyloid and fairly well-preserved groups of cortical cells. There is only slight involvement of the *Z. G.*; the cells of this zone appear normal. In places, long columns of fairly well-preserved epithelial cells of the *Z. F.* are seen dipping down from the *Z. G.* Large islands of cortical cells about the central vein of the medulla show extensive amyloid deposits. The medullary cells appear normal.

Case 3: T. F., no. 6,654. Male, age 36. Admitted March 7, 1929. Duration of pulmonary disease 6 years. Right-sided pneumothorax was instituted shortly after the onset of illness and continued for about 5 years, when it became complicated by empyema with bronchial fistula. Principal complaints on admission were excessive cough with purulent expectoration, weakness and

subfebrile temperature. The skin had a uniformly brownish appearance and scattered pigmentation could be seen over the forehead, cheek-bones and neck. The patient stated that he noticed the change in his appearance during the preceding year. Although the possibility of Addison's Disease was considered a contraindication to surgical measures, the empyema urgently required more radical treatment than mere tube-drainage, for there was no possibility for the collapsed lung ever to reëxpand. Accordingly, extrapleural thoracoplasty was performed in 3 stages at intervals of approximately 3 weeks. Following each operation, the patient had a rather stormy clinical course, but reacted fairly satisfactorily to stimulants and forced fluids. Anorexia, nausea, vomiting and diarrhoea became troublesome symptoms about 3 months before death. Cyanosis and a complete collapse of the circulation occurred suddenly on March 28, 1931, terminating fatally in 2 hours. The blood-pressure on admission was 110/80, and during the last 6 months averaged 80/50. The urine contained 1- to 2-plus albumin and a few hyaline and granular casts. The blood findings were of no special interest.

Anatomical diagnosis: Chronic fibroid tuberculosis with cavitation of right lung; nodular tuberculosis of left lung; atelectasis, right lung; amyloid disease of liver, spleen, kidneys and adrenals; encapsulated empyema of right pleural cavity.

Gross pathology: The right chest is distorted by thoracoplasty wound. The right lung is collapsed. An encapsulated purulent exudate is present in the upper part of the pleural cavity. The left lung contains many well-encapsulated caseous nodules. The spleen is normal in size. The cut-surface appears firm in consistence and is waxy. The liver is firm and waxy in appearance. The kidneys show a smooth capsule and a firm, translucent, pale, glassy cut-surface. The adrenals are unusually firm and somewhat enlarged.

Microscopic changes in the adrenals: Amyloid deposits occupy the greater portion of the *Z. F.* and the *Z. R.* A large part of the cortical cells in these areas is completely destroyed. Small strands of markedly atrophied cortical cells are seen lying between thick bands of amyloid deposits. Occasionally, small islands of well-preserved columns of epithelial cells are seen in areas in which the deposits are less marked. Amyloid is seen to occupy much of the inner *Z. G.*; the outer portion of this zone seems fairly well preserved and free from amyloid. Amyloid is seen in the walls of the veins of the medulla and in small cortical nests, which are seen about veins. The medullary tissue appears well preserved.

Case 4: W. W., no. 7,154. Male, age 36. Admitted December 3, 1930, with a history of pulmonary tuberculosis of 18 months' duration. He had been a sufferer from asthma for 31 years. Left-sided pneumothorax was instituted 6 months after a diagnosis was established, but this treatment had to be dis-

continued soon afterward on account of a pleural effusion. The examination on admission showed a well-nourished man, weighing 222 pounds, having a somewhat sallow complexion. The cardiovascular system seemed normal. Blood pressure, 150/90. The salient chest findings were a left-sided hydropneumothorax with upper-lobe fibrocavernous disease and extensive proliferation with early cavitation involving the right upper lobe. For a time the patient reacted to treatment satisfactorily, especially after the aspiration of fluid followed by phrenicectomy, but gradually he began to complain of weakness, and vague abdominal pains, with diarrhoea and progressive loss of weight. Six months prior to death, weakness became quite pronounced, associated with a painless diarrhoea. Gastrointestinal X-ray series were negative for tuberculous enterocolitis. Vomiting became quite frequent and had no relation to food, nor was it precipitated by coughing. Vomiting, diarrhoea and circulatory collapse were the terminal symptoms, with death occurring on April 23, 1933. The blood-pressure averages during the last month of life were 100/80, and the urine throughout residence contained 1- to 3-plus albumin with hyaline and granular casts. Pigmentation was not noted at any time, but the skin had a cachectic appearance with a tendency toward brownish discoloration.

Anatomical diagnosis: Chronic pulmonary fibroid and nodular tuberculosis with cavitation; tuberculous bronchopneumonia; amyloid disease of liver, spleen, kidney and adrenals.

Gross pathology: The left pleural cavity is obliterated by dense fibrous adhesions. The right lung contains many small firm nodules which, on section, are well encapsulated and contain firm yellowish-white centres. Many large and small cavities occupy the upper and lower lobes of the left lung. The intervening tissue shows tuberculous bronchopneumonia. The spleen is three times its normal size; the pulp is dark red and firm, and has a waxy, semitranslucent appearance. A small round ulcer with undermined edges is noted in the mucosa of the caecum. The liver weighs 2,300 gm. The surface is pale, gray-yellow in color, and firm. The substance cuts like tallow. Both adrenals appear large and firm. The kidneys are normal in size. They are pale in color.

Microscopic examination of the adrenals: There are thickly scattered patches of amyloid deposits, most numerous in the *Z. F.*, but also extending here and there into the *Z. R.* and *Z. G.* Between these areas small groups and columns of epithelial cells, fairly free from amyloid deposits, are noted. The cells of the inner *Z. F.* and the *Z. R.* contain a large amount of pigment. The medullary tissue appears well preserved.

Case 5: J. R., no. 7,581. Male, age 44. Admitted September 22, 1932, on account of progressive weakness, abdominal pains and diarrhoea. The onset of pulmonary tuberculosis dated back to 1917, but after one year of hospitaliza-

tion he improved sufficiently to be able to work until 1926, when the symptoms noted above became manifest and gradually increased in severity. *Physical examination:* The skin of the face and chest had a brownish color, which the patient attributed to heliotherapy. There was no other evidence of pigmentation. The height was 71 inches and the weight was 96 pounds. The pulse was rapid, ranging between 100 and 120 in bed; blood-pressure 116/76. The heart was markedly displaced to the right. Stethoscopic and X-ray findings disclosed fibrocavernous tuberculosis, involving the greater portion of the right lung and an apparently normal left lung. Gastrointestinal X-ray series were negative for tuberculosis. Asthenia became quite pronounced one month after admission, and the blood-pressure fell to 90/70. At the suggestion of Dr. James J. Waring, *Eschitan* (cortin) was administered in 1- to 2-cc. doses every other day for 2 weeks with apparent gain in strength and improvement in appetite. Insulin failed to produce such effects. On account of the prohibitive cost of the cortical extract, it was impossible to continue its use. Rapid emaciation followed. The last known weight, 2 months before death, was 83 pounds, but there occurred further loss in weight, as emaciation was extreme. Nausea and vomiting and extreme weakness were the terminal symptoms. The urine throughout residence showed 3- to 4-plus albumin with hyaline casts. Death occurred on July 19, 1933, the immediate cause being circulatory failure.

Anatomical diagnosis: Fibroid tuberculosis, with cavitation of right lung; disseminated tuberculosis of left lung; hypertrophy of right ventricle; amyloid disease of liver, kidney, spleen and adrenals.

Gross pathology: The body is markedly emaciated. The right ventricle is moderately hypertrophied; its thickest portion is 0.8 cm. The left lung is 800 gm. in weight. There are numerous, encapsulated caseous nodules throughout the lung. The right lung weighs 450 gm. The upper lobe shows a large, thick-walled cavity, 10 cm. in diameter, with trabeculated walls. There is marked fibrosis of the remaining portion of the upper and lower lobes. The liver weighs 2,375 gm.; its edges are round. The cut-surface is firm, pale and glassy. The spleen weighs 390 gm. It is firm and presents a waxy, translucent appearance. Both kidneys are enlarged, firm and extremely pale.

Microscopic examination of adrenals: The cortex is replaced for the most part by amyloid. A small rim of the *Z. G.* appears intact. The amyloid deposits extend through the entire layer of the *Z. F.* and *Z. G.*, causing marked destruction of the adrenal parenchyma. Only an occasional short column of the *Z. F.* in its outer portion appears intact.

A varying degree of pigmentation was present in 4 patients of this group; yet, in case 4 without any pigmentation, the gastrointestinal symptoms were more severe than in the other four cases. Another

interesting observation is the small solitary ulcer in the caecum which alone could hardly account for the intractable diarrhoea in case 4. The tuberculous bronchopneumonia was undoubtedly a terminal complication and played no rôle in the causation of symptoms earlier in the course of the disease. While amyloidosis of the liver, spleen and kidney could possibly account for many of the symptoms, the gastrointestinal manifestations and the asthenia were in all probability aggravated by the adrenal insufficiency. We have had occasion to observe the clinical course in two patients, in whom amyloid involvement of the liver, spleen and kidneys was found but the adrenals were spared. In these patients the symptoms were less severe and protracted over a longer period of time. While in cases 1 and 2 the associated tuberculous enterocolitis might have been in part responsible for the gastrointestinal symptoms, it is well known that many patients with more extensive involvement of the intestinal tract have not infrequently relatively few symptoms during life. The suddenness of death in cases 1 and 3 would tend to confirm the opinion that Addison's Disease played a considerable rôle in the symptomatology. The slight temporary improvement from a Muirhead regimen in case 1 and from cortical extract in case 5 would seem to constitute further corroborative evidence in favor of Addison's Disease, and opens an avenue for speculation whether such patients could be benefited by cortical extract to the same extent as frank, uncomplicated cases of Addison's Disease. While it is conceded that patients described in this group do not conform fully to the accepted clinical concept of Addison's Disease, it is conceivable that many of the clinical manifestations were due to destruction of the adrenal cortex and not entirely to the tuberculosis.

GROUP 2

Questionable Clinical Cases of Addison's Disease

Case 1: S. L., no. 6,347. Female, age 36. Admitted November 2, 1927, with a diagnosis of diabetes mellitus complicated by pulmonary tuberculosis of 5 years' duration. The pulmonary lesion was far advanced, bilateral, with major involvement of the left lung. The diabetes was readily controlled by a basic diet and insulin. In May, 1928, left-sided pneumothorax was induced, resulting in some improvement until October, 1928, when spontaneous pneumothorax occurred on the treated side, followed by empyema. Tube-drainage was instituted with gratifying results. The first manifestation of nausea and vomiting occurred in October, 1930, approximately 16 months' after the de-

velopment of the empyema. These symptoms became progressively worse, followed 6 months later by intractable diarrhoea. The liver at this time was about 4 fingers-breadth below the costal margin. All the clinical manifestations were attributed to amyloidosis, including the adrenals. Tuberculous enterocolitis was considered a possibility. There was no pigmentation. The blood-pressure on admission was 130/80, with averages during the last 6 months of 90/60. It was the marked asthenia and uncontrollable nausea and vomiting that gave rise to the suspicion of associated Addison's Disease. Death occurred on February 26, 1932.

Anatomical diagnosis: Chronic caseous tuberculosis of lung with cavitation and recent bronchopneumonic dissemination; tuberculous empyema; amyloid disease of liver, spleen, kidneys and adrenals; tuberculous ulceration of the ileum.

Gross pathology: The legs showed a marked pitting oedema. The left pleural cavity contains a large encapsulated accumulation of thick, greenish-yellow purulent material. The apex of the right lung contains a small thick-walled cavity. Throughout the lower lobes are many clusters of gray tubercles. The left lung is collapsed. A large cavity occupies the upper half of the upper lobe. In the lower lobe are several encapsulated caseous masses, varying from 1 to 2 cm. in size. The spleen weighs 250 gm. The cut-surface is homogeneous, pale reddish-brown, and glassy in appearance. The liver weighs 2,950 gm., and is grayish-yellow and exceedingly firm. The right adrenal is 12, and the left 10 gm. Both are normal in size but firmer than usual. The ileum contains several small discrete ulcers in the lower 50 cm. The kidneys are normal in size, but somewhat opaque and grayish-yellow.

Microscopic examination of the adrenals: The *Z. F.* is densely infiltrated with amyloid. Only an occasional strand of normal epithelium is seen. The deposits also involve to a great extent the *Z. R.* with marked destruction of the parenchyma. Most of the *Z. G.* is free from amyloid deposits, and appears well preserved. The medullary tissue appears free from amyloid.

Case 2: W. T., no. 6,400. Female, age 40. Admitted January 20, 1928. For 4 years prior to entrance she had been continuously treated in various institutions for pulmonary tuberculosis. Both physical and X-ray examinations disclosed extensive fibrocavernous disease throughout the right lung, with recent infiltration of the base of the upper lobe. The general and pulmonary condition improved, until finally most of the findings became localized to the right upper lobe. Comparative roentgen films showed remarkable clearance of the lesion on the left side and also of the lower lobe on the right, so that some form of collapse therapy was under advisement. However, acute intestinal symptoms became manifest about 6 months prior to death and became progressively worse, resulting in extreme loss of weight and marked asthenia. The

few freckles on the face, noted on admission, became more confluent, particularly over the forehead, and assumed a blotchy appearance of deep pigmentation. The blood-pressure averages were 80/60. The weight on admission was 98 lbs., and it was 80 lbs. one month after the onset of intestinal symptoms. Death occurred on May 13, 1930. Tuberculous enterocolitis was given as the immediate cause of death with a possibility of disease of the adrenals.

Anatomical diagnosis: Chronic pulmonary tuberculosis, bilateral, with cavitation in right upper lobe; tuberculous enteritis and colitis with ulceration; amyloid infiltration of spleen, liver, kidneys and adrenals.

Gross pathology: The body is emaciated. There is oedema of the lower extremities. The right pleural cavity is obliterated by dense fibrous adhesions. The upper lobe of the right lung is occupied for the most part by a large cavity. A small round cavity is present in the middle lobe. Numerous scattered caseous nodules are present in the lower lobe. In the left lung there are scattered caseous nodules. The spleen weighs 300 gm. Its cut-surface shows a typical "sago" appearance. The ileum and caecum show numerous tuberculous ulcers. The liver is considerably enlarged and presents a pale surface which is exceedingly firm. The kidneys and adrenals are normal in size, but are extremely firm.

Microscopic examination of the adrenals: Amyloid deposits are present in patchy distribution, mainly in the *Z. F.* In places, the entire thickness is involved; in other areas, only a portion is infiltrated with amyloid. Adjacent to the areas in which the amyloid deposits have destroyed the epithelial columns of the *Z. F.* are long columns of well-preserved cells which have little or no deposit of amyloid about them. The *Z. R.* and *Z. G.* show only scanty amyloid deposits. The medulla appears well preserved.

Case 3: R. K., no. 6,509. Male, age 37. Admitted July 6, 1928, on account of increasing weakness, nausea, vomiting and insomnia. The onset of pulmonary tuberculosis occurred in the winter of 1916, but after a brief period of sanatorium treatment the patient was able to work until a year prior to admission. The pulmonary lesion was of the fibrocavernous type, involving the left lung and a limited degree of infiltration at the right apex. The skin had a waxy color, not unlike that of cachexia seen in malignant tumor. The abdomen was moderately distended, with evidence of fluid in the peritoneal cavity. The aspirated fluid had the characteristics of a transudate and was negative for tubercle bacilli. The urine showed 1- to 2-plus albumin. The blood-chemistry was normal. The ascites was attributed to cardiorenal insufficiency. There was a moderate degree of secondary anaemia. The blood-pressure on admission was 110/80, and on February 1, 1929, 104/74. The terminal symptoms of extreme asthenia, nausea, vomiting and diarrhoea were attributed to amyloidosis involving probably also the adrenals.

Anatomical diagnosis: Chronic pulmonary tuberculosis with cavitation and tuberculous bronchopneumonia; old calcified tuberculous pleuritis; miliary tuberculosis of the liver, spleen, kidneys, pancreas, testes and mesenteric lymph nodes; amyloid infiltration of liver, adrenals, kidneys, pancreas, stomach, intestines and lymph nodes; anasarca.

Gross pathology: The body is extremely emaciated. There is marked oedema of both legs and thighs. The right pleural cavity is completely obliterated by dense adhesions. The upper lobe of the right lung is occupied by a large cavity with ragged walls. There are numerous solid grayish nodules in the lower and middle lobes. The left lung contains a small irregular cavity at the apex. A calcareous, caseous nodule, 1 cm. in diameter, is located in the lateral portion of the lower lobe. The spleen is twice normal size. The cut-surface shows numerous translucent spots which have a glassy appearance. There are also numerous small gray spots. The liver is enlarged to twice normal size, is firm, and its cut-surface is smooth, firm and waxy. Both kidneys are enlarged, thickened, pale and firm.

Microscopic examination of the adrenals: There is a diffuse and marked deposit of amyloid almost completely replacing the cells of the *Z. F.* and *Z. R.*, leaving only scattered clusters and columns of epithelial cells which show marked atrophy. The *Z. G.* is heavily infiltrated with amyloid in its inner portions; areas of *Z. G.* immediately beneath the capsule appear normal. Bands of cortical tissue about the central vein of the medulla show marked deposits of amyloid. An occasional small miliary tubercle is seen in the cortex. The medulla for the most part appears normal.

Case 4: R. M., no. 7,095. Female, age 28. Admitted September 20, 1930, with a history of pulmonary tuberculosis of 18 months' duration. The pulmonary lesion was of the fibroid type, with large cavitation in the right apex and recent infiltration, with an area of early excavation at the left apex. Following the administration of left-sided pneumothorax to control the recent and more active lesion, considerable improvement followed. One year after admission, she began to complain of increased weakness, distress after meals, occasional nausea and vomiting, and vague abdominal pains and diarrhoea. In January, 1932, diarrhoea became a troublesome symptom, followed by rapidly increasing asthenia and dyspnoea. The latter two symptoms could not be attributed to the pulmonary involvement. No pigmentation or discoloration of the skin was noted. Blood-pressure averages were 110/90 throughout residence. The urine was negative on admission, 2-plus albumin in October, 1932, and 4-plus during the last 6 months of life. Death occurred on May 6, 1933. The terminal symptoms were attributed to amyloidosis with possible adrenal involvement.

Anatomical diagnosis: Chronic pulmonary tuberculosis with cavitation; chronic duodenal ulcer; amyloid disease of adrenals, liver, spleen and kidneys.

Gross pathology: The body shows general anasarca. Small verrucae are present along the line of closure of mitral valve. The upper lobe of the right lung contains a large cavity partially filled with purulent material. Numerous tubercles surround the cavity. The lower lobes appear normal. The upper lobe of the left lung contains several small cavities. About these are many caseous nodules. The lower lobe shows no evidence of tuberculosis. A duodenal ulcer, 6 mm. in diameter, is present just below the pyloric ring. Its edges are indurated. The spleen is enlarged; the capsule is smooth. The cut-surface is mottled gray and red. The liver is enlarged and pale, and presents a glassy translucence. The kidneys present a coarsely granular surface. The cut-surface is light grayish-yellow in color and extremely firm. The adrenals appear normal.

Microscopic examination of the adrenals: Dense masses of amyloid are seen along the column of the *Z. F.*, causing marked destruction of the cortical cells in this layer. The outer *Z. F.*, the *Z. G.* and *Z. R.* are less involved. In these areas, the cells appear well preserved. Dense masses of amyloid are seen in the walls of large veins. The vessels in the deeper layers of the *Z. F.* and *Z. R.* are markedly dilated and congested.

Case 5: L. C., no. 7,176. Female, age 29. Admitted January 20, 1931. A diagnosis of pulmonary tuberculosis was made 2 years prior to admission, during which time she had been confined to bed practically all the time. The principal complaints, in addition to cough and expectoration, were progressive weakness, abdominal distress after meals and diarrhoea. The pulmonary lesion was confined principally to the left lung. Collapse therapy was impossible on account of pleural adhesions. More radical surgery was deemed inadvisable on account of the intestinal symptoms associated with marked weakness. Three months prior to death, which occurred on August 16, 1932, the abdominal symptoms became markedly accentuated followed by rapid emaciation. The skin had a sallow appearance; pigmentation was not present. There was no evidence of involvement of the right lung until 2 weeks prior to death. The urine was negative on admission, 1-plus albumin with a few hyaline casts in August, 1931, and 3-plus albumin in June, 1932. The average blood-pressure was 95/70.

Anatomical diagnosis: Chronic tuberculosis of the left lung with cavitation; acute tuberculous bronchopneumonia; multiple ulcers of the oesophagus; early tuberculosis of the colon (proved on microscopic examination as negative for tuberculosis); amyloid disease of kidneys, adrenals, liver and spleen.

Gross pathology: The body is markedly emaciated. The left lung is almost entirely converted into a thick-walled cavity extending from apex to base.

The contents consist of a chocolate-colored thick fluid. The right lung shows scattered clusters of tubercles throughout all lobes. The spleen weighs 125 gm.; it is exceedingly firm. The liver weighs 1,700 gm. and is pale and very firm. Both adrenals are firm but are normal in size and shape. The cortex of each is pale grayish-yellow. Both kidneys present a pale, coarsely granular surface. The cut-surface of the cortex is of a translucent grayish-white color.

Microscopic examination of adrenals: Amyloid is seen to occupy most of the inner two-thirds of the *Z. F.* and to a less extent the *Z. R.* The outer third of the *Z. F.* and the whole of the *Z. G.* is fairly free from amyloid deposits. In the areas which are densely infiltrated with amyloid, the adrenal parenchyma is destroyed. The medulla appears normal for the most part.

Pigmentation was noted in only one of these patients; hence, the diagnosis of symptoms of associated Addison's Disease was chiefly presumptive. Of the 5 patients in this group, 2 had tuberculous enteritis which might have been responsible for the intestinal symptoms, but it is believed that this pathological involvement was a terminal complication. Intestinal tuberculosis alone, unless it be of the acute and fulminating variety, rarely gives rise to such extreme asthenia, nausea and vomiting as noted in these patients. In 100 cases of intestinal tuberculosis with positive X-ray findings, R. J. Erickson (18) found that severe nausea was present in only 17 per cent and moderate to slight nausea in 35 per cent, making a total of 52 per cent. In the same group of patients, vomiting was present in only 37 per cent, whereas in all of our 5 patients the gastrointestinal symptoms were very severe and practically without any remission. It is possible that the amyloidosis of the stomach and intestines in case 3 was greatly if not solely responsible for marked digestive disturbances, but the asthenia and emaciation were so striking that it was impossible to escape the suspicion that destruction of the adrenals was a contributing factor.

Weakness in nephropathies, especially in nephrosis of either the degenerative or the toxic and necrotizing type, is at times quite evident, but rarely to the extent manifested by these patients. Not infrequently patients with nephrosis have a painless diarrhoea, which may be quite profuse, especially during the oedematous stage, and which is said to be due to increased permeability of the blood-vessels of the intestinal tract (19). In all of our patients in this group the diarrhoea preceded the appearance of oedema by many weeks or months, and in many instances the oedema did not become manifest until a few days before death. Whether amyloidosis of the kidney is capable of causing the same symp-

toms as nephrosis is a debatable question, but it is difficult to attribute the symptoms observed in our patients to renal amyloidosis in the light of available clinical knowledge. The blood chemistry in many of these patients showed no evidence of nitrogenous retention and even the phenolsulphonephthalein function test was, in most instances, within normal limits.

The duodenal ulcer found in case 4 did not give rise to symptoms during life characteristic of this disease. It is notable that in this case there was no necropsy evidence of tuberculous enteritis. In case 5 there were multiple ulcerations of the oesophagus and irregular ulcerations of the ileum, which, on microscopic examination, did not give the histological picture of tuberculosis. In only one section taken from the ileum was there noted an early solitary tubercle, probably the beginning of miliary invasion. Ulceration of the intestinal tract, as is well known, is not uncommon in Addison's Disease. It is not unlikely that the ulceration noted in this case was caused by the destruction of the adrenal cortex.

GROUP 3

Amyloid Degeneration of Adrenals Showing no Clinical Signs of Addison's Disease

Case 1: A. S., no. 6,717. Female, age 31. Admitted June 5, 1929. Duration of pulmonary tuberculosis 9 years. Physical examination and the roentgen findings disclosed a far-advanced lesion involving the entire right lung and the left upper lobe with extensive cavitation. There was a marked pallor, although the haemoglobin was 89 per cent (Sahli). The urine was negative and the blood chemistry was normal. On March 19, 1930, acute intestinal symptoms set in. A few days later there was also noted slight oedema of the face and ankles. At this time urinalysis showed large quantities of albumin and hyaline casts. The terminal symptoms were progressive weakness, nausea, vomiting, diarrhoea and rapid emaciation. Death occurred on April 5, 1930.

Anatomical diagnosis: Chronic pulmonary tuberculosis with cavitation, bilateral; tuberculous ulcers of colon; oedema of lower extremities; amyloid infiltration of spleen, adrenals, kidneys and liver.

Gross pathology: The body is markedly emaciated. The lower extremities show a marked oedema. The right pleural cavity is completely obliterated by firm adhesions. The right lung consists almost entirely of a large single cavity with very thin walls. The left lung contains scattered caseous nodules and an occasional calcareous nodule. Much of this lung is well aerated. The caecum contains many irregular ulcers with a maximal diameter of 1 cm. The

spleen is enlarged and firm. The liver is normal in size. Both kidneys are enlarged and very pale. The adrenals show no abnormality.

Microscopic examination of the adrenals: Dense masses of amyloid are seen along most of the columns of the *Z. F.*, causing marked destruction of the epithelial cells. The outermost portion of the *Z. F.* and most of the *Z. G.* appear uninvolved and show well-preserved parenchyma. The *Z. R.* shows marked destruction due to dense deposits of amyloid. No changes are noted in the medullary tissue.

Case 2: F. P., no. 6,726. Male, age 26. Admitted June 18, 1929, with a history of pulmonary tuberculosis of 16 months' duration. The examination disclosed a far-advanced, fibroulcerative lesion, involving the greater portion of the right lung and left upper lobe with bilateral cavitation. There was also subacute tuberculous laryngitis involving the epiglottis and arytenoids. The complexion was sallow and there was considerable emaciation. Three months after admission, diarrhoea, nausea and weakness dominated the clinical picture. The urine showed 4-plus albumin throughout residence. The blood-pressure on admission was 130/90 and on November 31, 1930, 120/30. Death, which occurred on December 29, 1930, was attributed to pulmonary and laryngeal tuberculosis and tuberculous enterocolitis.

Anatomical diagnosis: Chronic bilateral pulmonary tuberculosis with cavitation; tuberculosis of larynx and peribronchial lymph nodes; chronic tuberculous pleuritis; miliary tuberculosis of liver, spleen and kidneys; amyloid disease of spleen, adrenals, kidneys and liver.

Gross pathology: There is a marked degree of emaciation. Both pleural cavities are obliterated by dense firm adhesions. In the apex of the right lung is a large thick-walled cavity, 6 cm. in diameter. Several smaller cavities are present in the middle lobe. Scattered caseous nodules are seen in the lower lobe. Several small cavities are present in the upper lobe of the left lung. The lung tissue about these nodules contains numerous small white firm caseous nodules. The spleen is normal in size and shape. The cut-surface is smooth, dark red and somewhat translucent. The liver is normal in size, pale, and firmer than normal. Cut-surfaces of the kidneys are pale and waxy. The adrenals show no visible changes.

Microscopic examination of the adrenals: Amyloid is seen in patchy distribution, involving portions of the *Z. F.* Large areas of well-preserved columns are present between areas involved by amyloid. The *Z. R.*, *Z. G.* and medulla show little change.

Case 3: M. B., no. 7,063. Male, age 32. Admitted August 14, 1930. The onset of pulmonary tuberculosis occurred 7 years previously, during which time the patient was under conservative treatment without result. The ex-

amination showed fibrocavernous tuberculosis, involving the right upper lobe and slight infiltration of the left apex. The complexion was sallow. There was no pigmentation. There was moderate tachycardia; the pulse ranged between 100 and 120 in bed. The blood-pressure was 120/86. There was a moderate degree of dyspnoea and weakness. The latter was a complaint even during the time when the respiratory symptoms were in the background. Right-sided pneumothorax and phrenicectomy were of no value in controlling the frequently recurring haemoptyses. An upper-stage thoracoplasty was performed on February 18, 1932. The postoperative course was very stormy, dyspnoea and weakness being prominent features. Asthenia, dyspnoea and vomiting were the principal terminal symptoms, resulting in death on November 17, 1932. The urine showed 2-plus albumin with hyaline casts throughout residence. Blood-chemistry and phenolsulphonephthalein functional tests were normal.

Anatomical diagnosis: Chronic fibroid tuberculosis of the lungs with cavitation; hypertrophy and dilatation of the right ventricle; chronic passive congestion of liver, spleen and kidneys; amyloid disease of spleen, liver, kidneys and adrenals.

Gross pathology: The body is markedly emaciated. Both pleural cavities are obliterated by dense fibrous adhesions. The thickness of the right ventricle is 1 cm. There is a marked dilatation of this chamber. There is extensive fibrosis of both lungs. A thick-walled cavity, 2.5 cm. in diameter, is present in the left upper lobe. The lung is studded with small, hard, well-encapsulated nodules. The right lung contains a large cavity at the apex, 4 cm. in diameter. Two other cavities, slightly smaller than this, are present in the lower portion of the upper lobe. The lower lobes contain large numbers of scattered firm nodules. The spleen is firm, homogeneous and reddish-brown. The liver is pale and brown. Its cut-surface presents a nutmeg appearance. The parenchyma is very firm. No changes are noted in the kidneys or adrenals except for marked congestion of the former.

Microscopic examination of the adrenals: Amyloid is found unevenly deposited in the inner two thirds of the *Z. F.* and portions of the *Z. R.* Long columns of the *Z. F.* show well-preserved cortical cells. The cells of the *Z. R.* also appear normal. No changes are noted in the medullary cells.

Case 4: W. K., no. 7,099. Male, age 26. Admitted September 23, 1930, with a diagnosis of pulmonary tuberculosis of 4 years' duration. The physical findings pointed to far-advanced, bilateral, fibroulcerative tuberculosis with cavitation on the right side involving the entire upper lobe and scattered infiltration of the left upper lobe. There was also a costosternal abscess and a suspicion of a psoas abscess on the right side. The patient's face had a sallow, somewhat muddy appearance, usually not seen in uncomplicated cases of

chronic pulmonary tuberculosis. The blood findings were essentially normal. The urine showed 1-plus albumin throughout residence. On account of recurring haemoptyses, right-sided pneumothorax was instituted on October 23, 1930, without effecting a good collapse on account of pleural adhesions. Progressive dyspnoea and weakness became manifest in February, 1931. There were no gastrointestinal symptoms. Death occurred on April 29, 1931, and was attributed to what appeared to be cardiac failure.

Anatomical diagnosis: Chronic bilateral pulmonary tuberculosis with cavitation; Pott's disease; amyloid disease of liver, spleen, kidneys and adrenals; tuberculosis of the adrenals.

Gross pathology: There are several cavities in the right upper lobe, 1 to 4 cm. in diameter and surrounded by caseous and calcified nodules. Two cavities are present in the left upper lobe, 1 cm. and 2 cm. in diameter, respectively. A few calcified nodules are present in the lower lobe. The body of the 7th thoracic vertebra is necrotic. A paravertebral tuberculous abscess extends along the bodies of the 6th, 7th and 8th thoracic vertebrae. The spleen is normal in size but presents a mottled surface suggestive of "sago" spleen. The liver is normal in size. Its cut-surface is firm, waxy and pale, and its substance cuts with increased resistance. The adrenals appear normal.

Microscopic changes in the adrenals: Amyloid is seen in patchy distribution involving most markedly the inner portion of the *Z. F.* Large areas of the cortex appear normal. In places, amyloid involves the thickness of the *Z. F.* and *Z. R.*, and occasionally extends into the *Z. G.* There are scattered miliary tubercles in the medulla and cortex.

The extensive amount of tuberculosis and the rapid course seemed to account for all the clinical manifestations in the patients of this group. In none of these cases was amyloidosis suspected. In case 1, acute toxic nephrosis was considered a possibility complicated by tuberculous entercolitis. In case 2, the intestinal symptoms seemed to be fairly characteristic of tuberculous enterocolitis. The fairly well-sustained blood-pressure was somewhat misleading, although it was recalled that frank cases of Addison's Disease may have a high blood-pressure. In cases 3 and 4, the terminal symptoms were in no way suggestive of adrenal insufficiency. This fact, however, emphasizes the necessity of considering the possibility of amyloidosis, including that of the adrenals, in every case of advanced pulmonary tuberculosis of many years' duration. Such an attitude might deter the clinician from resorting to radical therapeutic procedures which, instead of helping the patient, very frequently aggravate the clinical course and hasten death.

DISCUSSION OF PATHOLOGICAL CHANGES

In amyloid disease, the adrenals are moderately enlarged, although in some cases the organs are normal in size or smaller than normal. The normal shape is usually well retained. The organs are unusually firm and cut with increased resistance. The cortex is grayish-yellow or grayish-white. The medulla appears normal. In some cases the cortex presents a translucent glassy appearance similar to that seen in the kidney and spleen in amyloid disease. In cases in which the amyloid deposits are moderate in amount, the cortex may show a fine mottling of gray and yellow.

The microscopic changes were studied after staining with methyl-violet, Mallory's aniline-blue, acid-fuchsin and Foot's modification of Hortegas's silver-carbonate method counterstained with vanGieson's.

In the very mild cases of amyloid infiltration of the adrenals (figure 1) the deposits are seen most abundantly in the inner *Z. F.* as scattered masses or clumps of hyaline material. Small scattered areas of amyloid deposits may be seen also in other portions of the *Z. F.* and *Z. G.* Large areas of well-preserved cortical tissue are seen which show no amyloid about them.

In the adrenals, the seat of moderately advanced amyloid infiltration (figure 2), the hyaline material is fairly diffusely distributed in the inner two-thirds of the *Z. F.* and involves a large portion of the *Z. R.* The outer portions of the *Z. F.* and *Z. G.* contain only traces of amyloid. Here, also, fairly abundant amounts of cortical tissue free from amyloid deposits may be seen.

FIG. 1. SHOWING SLIGHT DEPOSITS OF AMYLOID IN CORTEX

FIG. 2. SHOWING MODERATE DEPOSITS OF AMYLOID, MOST MARKED IN THE INNER TWO ZONES

FIG. 3. SHOWING MARKED DEPOSITS OF AMYLOID, ALMOST COMPLETELY REPLACING THE GLANDULAR TISSUE

FIG. 4. APPEARANCE OF PATIENT IN POSITIVE GROUP (SEE CASE 5, GROUP 1), ILLUSTRATING EXTENSIVE EMACIATION ENTIRELY OUT OF PROPORTION TO EXTENT OR ACTIVITY OF PULMONARY LESION

FIG. 5. X-RAY FILM OF SAME CASE

Note extensive fibrosis of right lung with upper-lobe cavitation. Left lung relatively uninvolved.

FIG. 6. GROSS SPECIMEN OF RIGHT LUNG OF SAME CASE, SHOWING MARKED FIBROSIS WITH NO ACTIVE TUBERCULOUS INVOLVEMENT EXCEPT AT THE APEX, WHERE CAVITATION WAS PRESENT

FIG. 1

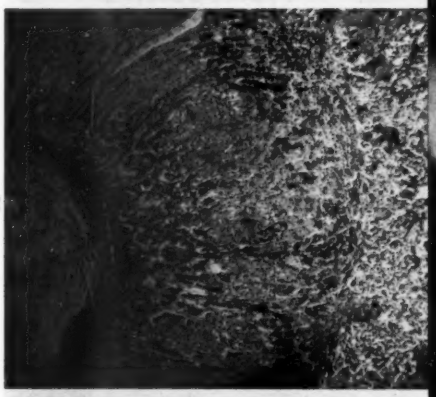

FIG. 2

FIG. 3

FIG. 4

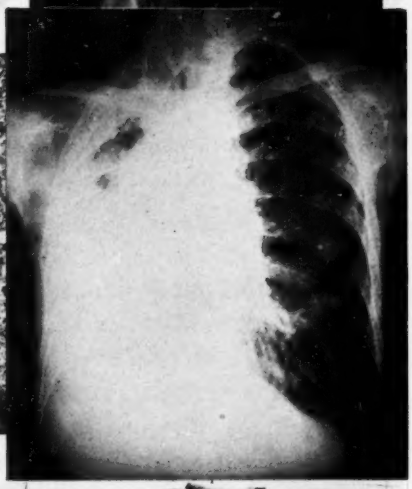

FIG. 5

FIG. 6

In the adrenals showing marked amyloid deposits, the infiltration diffusely involves the entire *Z. F.* and *Z. R.* The inner half of the *Z. G.* is also involved (figure 3). Very few normal cortical cells are seen in these portions. The *Z. G.* in its outer layer may show clusters of cortical cells which are well preserved.

The medullary tissue is not affected except in the area in which nests of cortical cells are present, principally, about the central vein. Amyloid is also seen in the walls of small and medium-sized vessels.

With Foot's modification of Hortegas's silver-carbonate method, counterstained with vanGieson's stain, the microscopic relationships of amyloid deposits to the endothelium, reticulum and cortical cells are best studied. The amyloid is stained a light, homogeneous gray color, the reticulin fibrils a jet-black color, and the cytoplasm of the cortical cells a bright yellow. The amyloid deposits are situated outside of the endothelial cells lining the capillaries and sinuses of the cortex and in intimate association with the reticulin fibrils (formerly the basement membrane). In places, large homogeneous masses of amyloid are seen lying between the reticulin fibrils and the epithelial cells. In other areas, the reticulum is broken up into extremely delicate arborizing networks of fine black staining fibrils which ramify throughout the amyloid. Most of these fibrils are fragmented and discontinuous. No amyloid can be seen within the cytoplasm of the endothelial cells or in the cytoplasm of the cortical cells. The amyloid often completely invests the epithelial cells of the cortex. Marked atrophy of these cells is seen in cases in which thick layers of amyloid are present. In many cases these cells have undergone complete degeneration, their places occupied by cellular débris and amyloid. The sinuses, especially in the inner *Z. F.* and the *Z. G.*, are often dilated and filled with blood, despite the presence of thick amyloid deposits beneath the endothelium. This condition was also noted by Bell (20) in amyloid infiltration of the renal glomeruli.

In an effort to determine whether or not a correlation existed between the degree of amyloid deposits and symptomatology, the adrenal glands were graded according to the extent of amyloid infiltration without previous knowledge of the clinical course. The glands were divided into three groups, according to the degree of amyloid infiltration of the cortex: first, showing slight deposits; second, moderate; and, third, marked deposits. A description of these three stages has been given a page or two above.

The following table shows the relationships between the degree of amyloidosis of the adrenals and the clinical groups:

DEGREE OF AMYLOID INFILTRATION	POSITIVE CASES GROUP 1	DOUBTFUL CASES GROUP 2	NEGATIVE CASES GROUP 3	TOTAL
Mild degree	0	0	2	2
Moderate degree	2	3	1	6
Marked degree	3	2	1	6
Total	5	5	4	14

Although the number of observations is small, it is apparent that, in those cases in which clinical symptoms of Addison's Disease were recognized (group 1), the extent of amyloid infiltration is greater than in cases in which the clinical features of Addison's Disease were doubtful (group 2) or absent (group 3).

SUMMARY AND CONCLUSIONS

In a series of 100 tuberculous patients that came to autopsy, 18 cases of amyloid disease were found. Of these, 14, or 78 per cent, showed also amyloid infiltration of the adrenals, involving mainly the cortex. A clinical classification of these patients independent of the pathological study resulted in their classification into three groups. In the "Positive" group there were 5 patients upon whom a diagnosis of Addison's Disease was made during life. Of these, 1 patient was temporarily benefited by the administration of cortical extract and another patient by the Muirhead regimen. In the second group, there were suggestive symptoms of Addison's Disease but a diagnosis was not warranted, and the third group did not show any symptoms of Addison's Disease during life. Histological study of the adrenals in those cases seems to show a definite relationship between the extent of amyloid involvement of the adrenal cortex and the symptomatology, notably the asthenia and gastrointestinal symptoms. Attention is called to the possibility that in many cases of far-advanced pulmonary tuberculosis there are symptoms of Addison's Disease which are usually unrecognized and attributed to the existing tuberculosis. The recognition of these symptoms should prove helpful, not only by way of therapy when cortical extract becomes available commercially, but also to prevent the institution of surgical procedures which invariably hasten a fatal termination in such cases.

In the light of this study, amyloid of the adrenals, which, as a rule, involves the cortex only, should be given a better recognized position in the aetiology of Addison's Disease.

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PULMONARY ASBESTOSIS

Report of a Case with Necropsy Findings[1]

DAN S. EGBERT

In view of the increasing incidence of pulmonary asbestosis as an industrial hazard, a report of the anatomical findings in a case is of interest, especially so since a clinical diagnosis was established three years before death and the case reported by Dr. Willard B. Soper (1). Moreover, there is relatively little in the literature on this subject in contrast to other forms of pneumonoconiosis.

That the asbestos industry is growing rapidly and that, as a result, pulmonary asbestosis will continue to become more important is seen from the fact that the total world production of asbestos increased from 96,490 tons in 1910 to 434,938 tons in 1929 (2).

Case Report[2]

S. K.: A 30-year-old white male, was admitted to William Wirt Winchester Hospital, May 26, 1929, with complaint of difficulty in breathing. Patient stated that he began work in an asbestos factory 13 years before at age 17 and continued in the industry from then on, being employed chiefly in the carding-room. Onset of present illness in autumn of 1928 with dyspnoea and some malaise. In February, 1929, following exposure to smoke in a factory fire, patient noticed his sputum streaked with blood, but frank haemoptysis was never experienced. Dyspnoea gradually increased in severity even after patient gave up work and at this time he also complained of burning pain in chest.

On admission to hospital, patient weighed 142 lbs. but was fairly well nourished and appeared somewhat pale. Skin cyanotic on pressure; an asbestos "corn" present on right hand. Thorax, well-formed and symmetrical, expanded equally on both sides, 5 cm. at the nipple line. Some dulness to percussion over apices, more marked on right. A few, dry, crackling, superficial râles heard over entire chest, also more marked over upper right lung. Roentgenographic examination showed shadows suggesting apical pleurisy, densities of marked bilateral diaphragmatic pleurisy, and a fine type of shadowing more marked over lower two-thirds of both lungs, with fine cobweb-like striations

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[2] The patient was under the care of Dr. G. M. Craig, Middletown, Connecticut.

extending out from both hilar regions. Diagnosis of pulmonary asbestosis made. On July 2, 1929, about one month after admission, patient was discharged with slight subjective improvement. When seen nine months later (April 9, 1930), even an effort at conversation produced shortness of breath. Epigastrium moved forward strikingly during inspiration; chest expansion at nipple line was reduced to 1.5 cm. Vital capacity 1,350 cc. From this time on, cyanosis became steadily more noticeable, especially on exertion. Gradually the chest expansion dropped almost to zero and breathing became more and more diaphragmatic. Death occurred suddenly, September 24, 1932, sixteen years after patient's beginning work in asbestos factory, four years after onset of symptoms, and three and one-half years after discontinuing work in this industry.

Necropsy: Limited to examination of thoracic contents. Body 173 cm. in length and weighed 65 kg. Thin but not emaciated. No oedema. Skin quite pale. Lips cyanotic. Posterior cervical lymph nodes barely palpable. No definite clubbing of fingers. On right hand, between thumb and index finger, was a round, smooth, firm, pale pink, slightly pedunculated nodule about 1 cm. in diameter.

Pleural cavities completely obliterated by firm, fibrous adhesions. Inner transverse diameter of thorax 27 cm.; that of heart 16 cm. Due to extensive pleural adhesions, parietal pleura and diaphragm were removed with lungs. About 200 cc. of thin, clear, light yellow fluid in the peritoneal cavity. Peritoneal surface of right diaphragm, attached to liver by some fibrinous adhesions, showed numerous subserous haemorrhages up to 1 cm. in diameter.

Lungs retained their shape well and were quite firm and noncrepitant (figure 1). Dense fibrous adhesions bound together the interlobar surfaces. Tracheobronchial lymph nodes slightly enlarged, some measuring 1.5 cm. in greatest diameter; uniformly dark red externally and on section. A few of smaller nodes showed black pigmentation. Calcified lymph node in upper lobe of right lung near hilum. Both lungs leathery. Entire upper lobe of right and apex of left lung were dry, firm, unyielding, noncrepitant, and mottled black and gray. Remainder of lungs mottled red and gray and firmer than usual. Scraping sectioned surfaces produced sound as of leather.

Smear of the fresh lung examined under microscope showed large numbers of asbestosis bodies. Histological preparations from lungs disclosed asbestosis bodies in both the greatly thickened pleura and lung tissue proper (figure 2). These were dark yellowish-brown, translucent, somewhat refractile and variable in shape. The most common form resembled a gnarled club, consisting of a round head, 15 to 20 micra in diameter, and an elongated tail, usually nodular or segmented, but frequently smooth or pointed. Occasionally the bodies were dumb-bell shaped, with elongated stem joining two rounded heads.

In some of them a core could be distinguished extending through entire length. This core more refractile than rest of body, and practically colorless or tinged red. The ends of these fine refractile cores within the rounded heads of asbestosis bodies were frequently pointed. One asbestosis body was seen to consist of a long, colorless, refractile, thread-like spicule, having round, dark yellowish-brown granules, about 2 micra in diameter, strung along it in bead-like manner. Small, fine, black pigment granules were associated with the

FIG. 1. LONGITUDINAL SECTION OF LUNGS SHOWING PULMONARY ASBESTOSIS

asbestosis bodies in most places. Large numbers of mono- and multinuclear phagocytic cells appeared throughout the pleura and pulmonary tissue, particularly about the asbestosis bodies. Frequently they had completely engulfed these bodies and the fine, black pigment granules. In one alveolus, there was a multinucleated giant cell, containing at least 8 asbestosis bodies and an asbestos spicule (figure 3). A number of red blood cells, some serous fluid and a few phagocytic cells and asbestosis bodies were present in most alveoli. Around the bronchioles and bronchi was an increase of dense, hyalinized fibrous connec-

FIG. 2

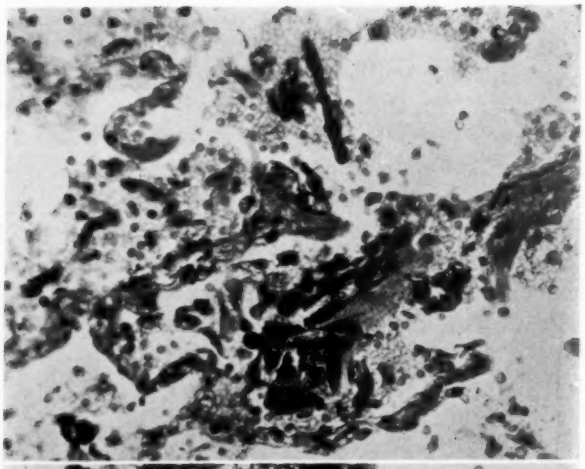

FIG. 3

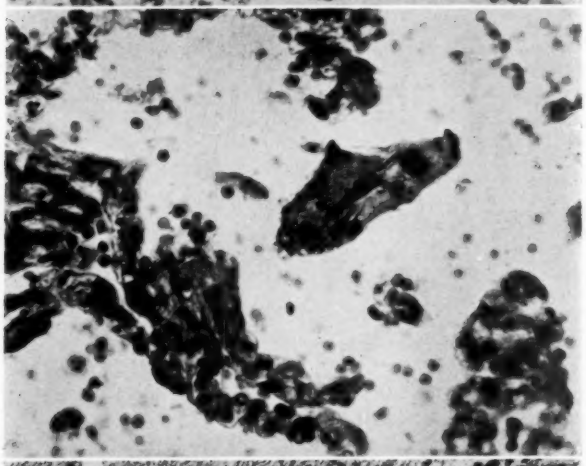

FIG. 4

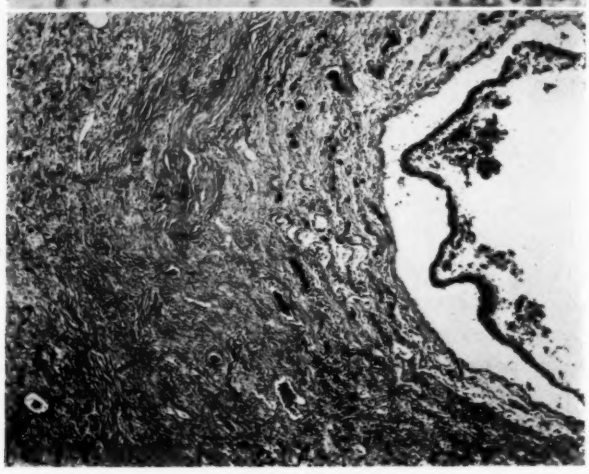

FIG. 2. ASBESTOSIS BODIES. × 266

FIG. 3. ASBESTOSIS BODIES IN FOREIGN BODY GIANT CELL. × 366

FIG. 4. UPPER LOBE OF RIGHT LUNG SHOWING DENSE FIBROSIS. × 36

tive tissue, containing asbestosis bodies, anthracotic pigment and phagocytic cells. Here and there occurred a perivascular small round-cell infiltration.

Preparations from upper lobe of right lung showed mostly dense, fibrous connective tissue in which asbestosis bodies were scarce (figure 4). Here and there were remains of alveoli represented by groups of small spaces lined with flat or cuboidal epithelium. Collections of small round cells lay about these spaces and in surrounding connective tissue.

Preparations of the tracheobronchial lymph nodes showed proliferation of reticular tissue, many collections of black pigment granules, very few asbestosis bodies, a large number of plasma cells and some large mononuclear cells. The black pigment granules were similar to those in lungs and were more numerous in hilar region than at periphery.

Heart weighed 375 gm. In right ventricle, which was dilated, the papillary muscles were large, trabeculae carneae prominent, and their interspaces wide and shallow. Apex of heart made up equally of both ventricles. All cardiac orifices and their valves appeared intact. Wall of right ventricle 6 mm. thick and that of the left 11 mm.

COMMENT

The history of asbestos and the clinical features of asbestosis have been presented by Soper (1) and will not be considered here. The morphological differentiation of asbestosis from other forms of pneumonoconiosis rests upon the evidence of characteristic asbestosis bodies, and on the type and distribution of the pulmonary fibrosis; namely, it is diffuse, with a tendency to be more marked around the bronchioles. This is in distinct contrast to the well-circumscribed, dense, hyalinized nodules of connective tissue seen in silicosis, in which condition the nodules form around and in the intrapulmonary lymphoid tissue, especially in the subpleural zone and in the tracheobronchial lymph nodes. As explained by Gardner and Cummings (3) in their experimental work, asbestos fibres, unlike other dusts, do not (after an exposure of two years in laboratory animals) penetrate into the ultimate divisions of the primary units of the lungs, but the major part of them come to rest in the respiratory bronchioles. Lymph-stasis, an important feature in the pathogenesis of silicosis, plays little, if any, rôle in asbestosis. Although the lymphatic channel of escape is apparently open to the cells containing asbestos fibres, they do not migrate to these vessels.

A review of the literature revealed the reports of 28 cases (including the present one) of pulmonary asbestosis with fatal terminations. These are listed in table 1.

TABLE 1

Summary of reported fatal cases of pulmonary asbestosis

CASE	REFERENCE	AGE	SEX	TIME EXPOSED BEFORE ONSET OF SYMPTOMS	TOTAL TIME EXPOSED	PRINCIPAL FINDINGS
1	Murray, M.: Charing Cross Hospital Gazette, 1900.	34	M	—	15 years	Extensive pulmonary fibrosis; no evidence of tbc.; asbestosis bodies in lungs.
2	Fahr, T., and Feigel: Deutsch. med. Wchnschr., 40: 1548–1549 (July 23) 1914. Further comment: Fahr, T.: Klin. Wchnschr., 11: 1114 (June 25) 1932.	—	—	—	—	Chronic indurative pneumonia; asbestosis bodies in lungs; quantitative increase of iron in lungs.
3	Cooke, W. E.: Brit. M. J., 2: 147, (July 26) 1924. Further comment—Cooke, W. E., and Hill, C. F.: J. Roy. Micr. Soc., 47: 232–238, (Sept.) 1927. Cooke, W. E.: Brit. M. J., 2: 1024–1025, (Dec. 3) 1927. McDonald, S.: Ibid., 1025.	33	F	Short time	18 years	Pulmonary fibrosis, particularly right lung; tbc. present; asbestosis bodies in lungs.
4	Simson, F. W.: Brit. M. J., 1: 885–887, (May 26) 1928.	—	M	—	1 year	Acute tbc. with associated fibrosis; fibrous process not associated with tbc.; asbestosis bodies in fibrous tissue of lungs.
5	Ibid.	—	M	—	2 years	Pneumonia 1 year before death which may have become organized; pleural adhesions; tracheobronchial nodes enlarged and hard; lungs hard and fibrous; no tbc.; asbestosis bodies throughout lungs.
6	Ibid.	—	—	—	—	Lobar pneumonia; slight connective-tissue increase in lungs; asbestosis bodies in lungs.
7	Ibid.	—	—	—	—	Lobar pneumonia; little connective tissue increase in lungs; asbestosis bodies in lungs.
8	Stewart, M. J.: Brit. M. J., 2: 509, (Sept. 15) 1928.	34	F	—	16 years	Extensive fibrosis and anthracosis; no tbc.; asbestosis bodies throughout lungs.

9	Wood, W. B., and Page, D. S.: Tubercle, 10: 457–460, (July) 1929.	34	F	5 years	9 years	Bronchopneumonia; diffuse fibrosis, particularly right lower lobe; arrested tbc. apparently having no influence on course of disease; asbestosis bodies throughout lungs.
10	Haddow, A. C.: Brit. M. J., 2: 580–581, (Sept.) 1929.	34	F	—	20 years	Chronic pulmonary fibrosis; no tbc.
11	Ibid.	48	F	—	24 years (estimated)	Pulmonary fibrosis and tbc. (No autopsy.)
12	Ibid.	34	M	—	13½ years	Bronchopneumonia; advanced pulmonary fibrosis; no tbc.
13	Ibid.	41	F	—	19 years	Advanced pulmonary fibrosis; no tbc.
14	Wood, W. B, and Page, D. S.: Tubercle, 11: 157–158, (Jan.) 1930.	21	F	About 12 months	15 months	Tuberculosis; caseous tubercles with numerous cavities involving chiefly upper two-thirds of both lungs; asbestosis bodies throughout lungs from apparently unaltered asbestos fibres to typical golden-yellow bodies.
15	Merewether, E. R. A.: J. Industr. Hyg., 12: 198–222, (May); 239–257, (June) 1930.	36	M	—	18 years	Advanced pulmonary fibrosis; no tbc. (No autopsy.)
16	Mills, R. G.: Minnesota Med., 13: 495–499, (July) 1930.	58	M	—	Not definite	Death occurred at least 17 years after cessation of exposure to asbestos dust; congestive heart failure; generalized pulmonary fibrosis; healed pulmonary tbc.; asbestosis bodies in lung.
17	Lynch, K. M., and Smith, W. A.: Jour. Am, Med. Ass., 95: 659–661, (Aug. 30) 1930.	—	M	—	28 months	Gunshot wounds; definite increase of fibrous tissue along course of blood-vessels and bronchioles; no tbc.; asbestosis bodies throughout lungs.
18	Ibid.	—	M	—	4½ years	Lobar pneumonia; pneumonia right lung and upper lobe of left; no tbc.; asbestosis bodies throughout lungs and in peribronchial lymph nodes.
19	Lynch, K. M., and Smith, W. A.: Amer. Rev. Tuberc., 23: 543–660, (June) 1931.	40?	M	—	17 years	(No autopsy.)

TABLE 1—*Concluded*

CASE	REFERENCE	AGE	SEX	TIME EXPOSED BEFORE ONSET OF SYMPTOMS	TOTAL TIME EXPOSED	PRINCIPAL FINDINGS
20	Ibid.	51	M	2 to 4 years	12 years	Pulmonary fibrosis of upper lobes of both lungs and lower lobe of left; no tbc.; asbestosis bodies throughout lungs.
21	Buresch, A.: Deutsche med. Wchnschr., 57, 1: 1100–1102, (June 26) 1931; 57, 2: 1247–1249, (July 17) 1931.	47	M	24 years	26 years	Right ventricular insufficiency; pulmonary fibrosis; tracheobronchitis; bronchopneumonia; no tbc.
22	Seiler, H. E., and Gilmour, M. D.: Brit. M. J., 1: 1112–1114, (June 27) 1931.	—	M	Few months	23¼ years	Heart failure; pulmonary fibrosis involving particularly right lung; no tbc.; asbestosis bodies throughout lungs, a few in peribronchial lymph nodes.
23	Beintker, E.: Arch. f. Gewerbepath. u. Gewerbehyg., 2: 345–358, (July 6) 1931.	—	M	20 years	20 years	Heart failure; pulmonary fibrosis; no tbc.; asbestosis bodies in lungs.
24	Ibid.	—	M	—	—	Heart failure; asbestosis bodies in lungs.
25	Stewart, H. L., Bucher, C. J., and Coleman, E. H.: Arch. Path., 12: 909–916, (Dec.) 1931.	—	M	—	9 years	No tbc.; asbestosis bodies present in alveolar walls.
26	Ibid. Further comment—Gordon, B., Jr.: Penn. M. J., 35: 637–639, (June) 1932.	55	M	—	9 months	Bronchopneumonia; diffuse fibrosis involving particularly lower lobes; tbc. throughout lungs with cavitation; asbestosis bodies throughout lungs, a few in bronchial lymph nodes and spleen.
27	Stewart, M. J., Tattersall, N., and Haddow, A. C.: Jour. Path. & Bact., 35: 737–741, (Sept.) 1932.	31	F	8 years	11 years	Bronchopneumonia; diffuse fibrosis involving most of basal portion of lower lobes of both lungs; tbc. in pleura but not in lungs; asbestosis bodies throughout lungs.
28	Soper, W. B.: Amer. Rev. Tuberc., 22: 571–584, (Dec.) 1930. (Present case.)	33	M	12 years	13 years	Cardiac failure; diffuse fibrosis of lungs involving particularly upper lobe of right and portion of upper lobe of left; arrested tbc.; asbestosis bodies throughout lungs; few in tracheobronchial lymph nodes.

In the 18 cases in which death seems to have been primarily the result of pulmonary fibrosis due to the inhalation of asbestos dust, the following may be observed: All were workers in asbestos factories; 9 of the 14 with age reported were between 31 and 36 years of age; the time of exposure to the dust before the onset of symptoms, when reported, averaged 9 years, and the total time of exposure, when reported, averaged 16 years.

Active pulmonary tuberculosis was present in 6 instances of the total 28 cases; the fatal outcome was primarily the result of tuberculosis in 3 instances.

One finding in asbestosis which has contributed as much as anything to the interest in the condition is that of the asbestosis bodies. Gloyne (4) has given excellent descriptions and illustrations of these bodies, and has summarized our present knowledge, as well as theories, concerning their formation. By placing the asbestosis bodies in concentrated sulphuric acid he showed that the golden-yellow material dissolved, leaving the fine, colorless, refractile cores which are apparently asbestos fibres (5).

There has been considerable discussion as to the origin of the enveloping yellow material. Cooke (6) (7) (8) considered the bodies to be of nonmineral origin, and thought that they consisted of central nuclei of asbestos spicules upon which formed colloidal aggregates of blood-protein plus, possibly, soluble fractions of asbestos. Gardner and Cummings (3) presented evidence that the asbestosis body is a derivative of the crystalline asbestos fibre which has been oxidized and hydrolyzed to a golden-yellow amorphous structure. They were able to reproduce the structure of the asbestosis body quite closely in the following manner: iron-free asbestos fibres were impregnated with an iron salt by heating them to dryness in a dilute ferric-chloride solution and were then ignited; these were then placed in a solution of sodium silicate; the iron salt, adhering to the fibres, reacted rapidly with the silicate to produce a curiously shaped golden-yellow structure which very closely resembled the asbestosis body.

It is interesting to note that although Gardner and Cummings were able to produce typical asbestosis bodies in guinea pigs by exposure to asbestos dust for 90 days, they could produce none in rabbits even after an exposure of 330 days.

Schuster (9) reported the findings at necropsy of a 10-year-old dog that had lived most of its life in an asbestos factory. Fibrosis of the lungs and many naked asbestos fibres were found, but no typical as-

bestosis bodies. Marchand (10) reported the findings at necropsy of two patients: one, of a worker in a dye-factory and the other a stone-fitter; the lungs of both contained structures that resembled quite closely asbestosis bodies. Tylecote and Dunn (11) and Cooke (12) reported structures resembling asbestosis bodies in the lungs of a coal-miner, who, in each instance, gave no history of exposure to asbestos dust.

SUMMARY

1. The anatomical findings are presented of a case of asbestosis whose clinical features were reported by Soper in 1930.

2. A summary is given of 28 cases of pulmonary asbestosis with fatal termination as found in the literature.

3. In the apparently uncomplicated cases with fatal termination, it was determined that all were workers in asbestos factories; 9 of the 14 with age reported were between 31 and 36 years of age; the time of exposure to the dust before the onset of symptoms, when reported, averaged 9 years; and the total time of exposure, when reported, averaged 16 years.

4. Active pulmonary tuberculosis was found to have been present in 6 instances of the 28 cases reported. In 3 instances death was primarily due to tuberculosis.

5. The nature of asbestosis bodies is discussed.

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VITAMINE THERAPY IN INTESTINAL TUBERCULOSIS[1]

M. MAXIM STEINBACH AND MILTON B. ROSENBLATT

Tuberculosis of the intestines is the most common complication of far-advanced pulmonary tuberculosis. Its incidence has been estimated to range from 65 per cent, according to Fishberg (1), up to over 90 per cent, as reported by Engelsmann, Herxheimer, and Wiegert. The high mortality associated with this complication has been responsible for the introduction of numerous therapeutic procedures directed both toward the alleviation of symptoms and the healing of the intestinal ulcerations. Among the popular forms of treatment, which, however, have proved disappointing, are calcium-chloride injections, heliotherapy, and ultraviolet rays. The use of a variety of astringent medications has also been found ineffective. The most recent therapeutic contribution is the administration of diets rich in vitamines.

The first experimental work on the relationship between vitamines and intestinal ulceration was reported in 1919 by McCarrison (2), who found that birds fed on diets deficient in vitamine B developed atrophic changes in the upper intestine. Several years later, Grant (3) demonstrated that scorbutic diets given with excessive amounts of vitamine D brought about failure of regeneration in epithelium and underlying mucosa after injury. However, with an abundance of both vitamines C and D in the diet, large necrotic ulcers healed quickly and completely. An association between diets deficient in vitamines and increased susceptibility to tuberculosis was recently shown by Steinbach (4) in his work on the albino rat, and a direct relation between vitamine deficiency and tuberculous enteritis was demonstrated by Smith and McConkey (5) in experiments in which they fed tuberculous sputum to guinea pigs. The guinea pigs which were on a diet deficient in vitamine C, or vitamines A, C and D, developed intestinal tuberculosis in a large proportion of the cases. Of 37 animals so treated, 32 showed enteric involvement. In the group of 35 controls there were only 11 positive cases. Gardner (6) repeated the work of Smith and McConkey, using chickens. The fowls on a regular diet were fed avian tubercle bacilli for 6 months or longer without any

[1] From the Tuberculosis Division of the Montefiore Hospital, New York.

infection taking place. When the birds were put on a special diet of autoclaved polished rice deficient in practically all known vitamines, together with the biweekly germ feedings, they became infected and died in a few months. At autopsy the majority of them showed the characteristic picture of spontaneous avian tuberculosis.

In 1930, McConkey (7) published the results of an extensive clinical study on the value of vitamines in the treatment of intestinal tuberculosis. He selected a group of 50 patients with positive roentgen-ray diagnoses of intestinal involvement. He gave this group, in addition to their regular diet, three ounces of tomato juice (vitamines A, B, G and C) and one-half ounce of codliver oil (vitamines A and D), served ice-cold, after each meal. For controls he had an equal number of patients who were given ultraviolet radiation, and a smaller third group who were given palliative treatment only. All three groups consisted of patients with moderate or advanced pulmonary tuberculosis. The treatment was continued for several months after the gastrointestinal tract had become radiographically normal, or until all symptoms had disappeared. His results after a long period of treatment showed a greater improvement in the cases treated with vitamines than in those treated with ultraviolet. The patients who received neither of the specific treatments did most poorly. Inasmuch as their stay in the hospital was longer than that of the other two groups, a higher mortality would naturally be expected. McConkey concluded that the addition of codliver oil and tomato juice to the regular diet was adequate treatment for intestinal tuberculosis complicating pulmonary disease, and suggested that it might prove a means of preventing intestinal tuberculosis. Frimodt-Moller (8) used this treatment in India on 25 patients for a period of four months and obtained most encouraging results which strikingly confirmed McConkey's report. Buylla (9), in Spain, tried it on a small group of cases and found marked improvement in two out of six instances. Kline (10) used this method unsuccessfully on a group of 7 terminal cases, but felt nevertheless that vitamines were factors of cardinal importance in the treatment of intestinal tuberculosis. Brown and Sampson (11) recently stated that the codliver-oil and tomato-juice treatment has apparently cured many cases. Altogether, a fairly large number of cases with clinical improvement has been recorded. There have not been reported, however, any detailed anatomical studies showing actual healing of the intestinal ulcerations as a result of vitamine therapy. Such studies are very significant in the final evaluation of the therapy and are obviously

far more important and informative than clinical and radiographic considerations. It is with this thought in mind that we delayed publishing our results with vitamine therapy until a sufficiently large number of patients had come to necropsy.

The codliver-oil and tomato-juice treatment of intestinal tuberculosis has been in use at the Montefiore Hospital for about two and a half years. As far as possible, an attempt was made to select cases in the earliest stages of the disease. Although a large number of patients was chosen, our present study is confined to only sixteen, due to the fact that many were unable to tolerate the oil or did not take it regularly. With the exception of two patients who are still alive the entire study is based on pathological considerations.

Of the group of 16 patients there were 4 who had presented symptoms strongly favoring a diagnosis of advanced intestinal tuberculosis but who on autopsy showed no evidence whatsoever of recent or healed intestinal ulcerations. It was concluded that the diagnosis had been erroneous. Two of the patients had shown marked symptomatic improvement. One had taken the mixture for 12 months and the other for $2\frac{1}{2}$ months. It was naturally felt during the lifetime of these patients that the improvement of their abdominal symptoms was due to the effect of the vitamines on the intestinal ulcerations. This indicates the unreliability of conclusions based on clinical impressions alone. We are of the opinion that similar errors would have occurred had we used the roentgen-ray for diagnosis. Recent work (12) has shown that X-ray diagnosis is unreliable in over 50 per cent of cases.

A detailed analysis of the clinical course and pathological findings in the remaining 12 patients is listed in table 1.

The group of cases studied consisted of 7 women and 5 men, all of whom were in the third and fourth decades. The pulmonary disease in all instances was extensive and bilateral. The sputum was positive in every case. The clinical duration of the enteric symptoms before beginning the vitamine treatment varied, depending on the interval between the onset and the time of admission into the hospital. Thus, case F. R. had abdominal pain and diarrhoea for only 3 weeks before the institution of the high-vitamine diet, while case J. J. L. had an enteric history of 6 years' duration. Case J. L. presented no conclusive symptoms but was given the codliver oil for psychological reasons. A month after the treatment was begun mild enteric symptoms appeared. The length of treatment also varied greatly, and in most instances coincided with the

TABLE 1

Results obtained with vitamine therapy at the Montefiore Hospital

PATIENT (SEX)	AGE	TYPE AND DURATION OF PULMONARY LESION	COMPLICATIONS	DURATION OF INTESTINAL SYMPTOMS AND SIGNS BEFORE INSTITUTION OF TREATMENT					DURATION OF TREATMENT	IMPROVEMENT	PATHOLOGICAL REPORT OF INTESTINES
				Abdominal pain	Diarrhoea	Constipation	Tenderness	Rigidity			
R. H. (F)	22	Fibrocaseous, cavitary, 1 yr.	Tuberculosis of Larynx	1 yr.	1 yr.	1 yr.	R.U.Q. +	None	2 yrs.	None	Superficial ulceration in terminal ileum; numerous caseous ulcers in appendiceal mucosa; several ulcers in caecum.
J. L. (M)	32	Fibrocaseous, cavitary, 3 yrs.	Tuberculosis of Larynx	None	None	None	None	None	3 mos.	None	Small superficial ulcers in caecum, ascending colon, first portion of transverse colon.
J. Z. (M)	31	Fibrocaseous, cavitary, 3 yrs.	Tuberculosis of Larynx	2 mos.	2 mos.	None	R.L.Q. ++	None	1½ mos.	None	Adhesions about the ileum with stricture formation in lower portion. Large ulcers in ileum, caecum, and ascending colon. Serosal surface of ulcers studded with conglomerate tubercles.
M. P. (F)	36	Fibrocaseous, cavitary, 2 yrs.		1 mo.	1 mo.	None	R.U.Q. ++	++	3½ mos.	None	Extensive ulceration from jejunum to lower colon, especially at ileocaecal region. Serosa studded with caseous tubercles. Hyperplastic areas of mucosa between ulcers.

F. G. (F)	23	Fibrocaseous, cavitary, 5 yrs.	Tuberculosis of Larynx	4 mos.	4 mos.	None	R.L.Q. +	None	2 yrs.	Marked improvement in enteric symptoms and also in pulmonary and laryngeal lesions.	Patient is still in hospital under observation.
B. G. (F)	25	Fibrocaseous, cavitary, 3 yrs.		1 yr.	1 yr.	None	R.L.Q. ++	None	1 yr.	Complete disappearance of enteric symptoms. General pulmonary improvement also.	Patient is still under observation in the O. P. D.
J. J. L. (M)	31	Fibrocaseous, cavitary, 6 yrs.	Tuberculosis of Larynx	6 yrs.	6 mos.	None	None	None	1½ mos.	None	Extensive ulceration from jejunum to rectum. Ulcers of varying sizes and ages. Many stellate scars which are evidence of healed ulcerations.
N. O. (M)	27	Fibrocaseous, cavitary, 4 yrs.		6 mos.	6 mos.	None	R.L.Q. ++	++	1 mo.	None	Many small and large ulcers in small intestine. Serosal surface of ulcers studded with yellowish tubercles. Large irregular ulcers in caecum and rectum. Caecal serosa covered with flaky fibrinous material.
E. S. (M)	21	Fibrocaseous, cavitary, 4 mos.	Tuberculosis of Larynx	2 mos.	2 mos.	None	R.L.Q. +	None	10 mos.	None	Pea-sized indurated ulcers in duodenum. Superficial ulcerations of varying sizes in jejunum and ileum. Numerous millet-sized follicles in caecum and ascending colon beneath mucosa.

TABLE 1—*Concluded*

PATIENT (SEX)	AGE	TYPE AND DURATION OF PULMONARY LESION	COMPLICATIONS	DURATION OF INTESTINAL SYMPTOMS AND SIGNS BEFORE INSTITUTION OF TREATMENT					DURATION OF TREATMENT	IMPROVEMENT	PATHOLOGICAL REPORT OF INTESTINES
				Abdominal pain	Diarrhoea	Constipation	Tenderness	Rigidity			
B. H. (F)	23	Fibrocaseous, cavitary, 4 yrs.	Tuberculosis of Larynx	2 yrs.	5 mos.	5 mos.	R.U.Q. ++	None	4 mos.	None	Extensive ulceration of caecum; few ulcers in ascending colon.
F. R. (F)	23	Fibrocaseous, cavitary, 1 yr.		3 wks.	2 wks.	None	L.L.Q. ++	None	3 mos.	None	Few small follicular ulcers and tubercles in mucosa of ileum. Few follicular ulcers in caecum.
E. B. (F)	25	Fibrocaseous, cavitary, 4 yrs.		6 mos.	6 mos.	None	R.L.Q. ++	None	1½ mos.	None	Extensive ulceration of jejunum and ileum. Tubercles present on serosal surface of ulcers. Entire caecum and 2/3 of ascending colon ulcerated. Ulceration also present in transverse colon and descending colon.

duration of life after treatment was instituted. The shortest period in the series was one month, and the longest two years. Of the 12 cases, only two showed any improvement worthy of mention. The remaining ten pursued a progressive course downhill without any noteworthy alleviation of the intestinal symptoms, and eventually died. During the course of the illness many remissions were noted, but these were similar to those observed in all cases of intestinal tuberculosis, and could not be attributed to the instituted therapy. No relation was observed between duration of treatment and improvement, or between duration of illness before treatment and improvement. Cases B. G. and R. H. both had symptoms for one year. The former received the treatment for one year and improved greatly; the latter succumbed after 2 years of treatment. On the other hand, case F. G. improved greatly after 2 years.

The most interesting part of the study was the examination of the tuberculous intestines. If the premise promulgated by McConkey, Brown and Sampson, and the others, that codliver oil and tomato juice is a cure for intestinal tuberculosis is correct, then there should have been present evidence of marked healing of the ulcerations, particularly in the cases which had received the treatment for a considerable period of time. The postmortem findings are given in detail in the table. Invariably all the specimens of intestine showed recent tuberculous ulcerations in either the ileum, caecum, or ascending colon. This finding, in itself, apparently proves that the codliver-oil and tomato-juice mixture is neither a cure nor a preventive for enteric tuberculosis. Examination of the involved intestines revealed an almost negligible degree of healing. The case which presented the greatest amount of healing was J. J. L., whose intestines showed many stellate scars interspersed with recent ulcers. The fact that this patient gave an enteric history of 6 years' duration and was on the codliver-oil treatment for only six weeks favors the view that healing was spontaneous in origin and began long before the therapy was introduced. Spontaneous healing in intestinal tuberculosis has been reported by many observers. This condition was found by Rubin (13) (of the Montefiore Hospital) in 10 per cent of his series of 500 consecutive necropsies on tuberculous patients who died with intestinal ulceration. As was mentioned previously, there were two patients in our series who did remarkably well under the codliver-oil and tomato-juice treatment. It is noteworthy that in both instances there was an associated improvement in the pulmonary condition. In view of the experience with the other patients we are unable to state with any degree of positiveness whether the healing was due to the therapy or was spontaneous.

DISCUSSION

The wide discrepancy between our results in vitamine therapy and those obtained by some other workers requires explanation. One possible source of this disparity is the likelihood that not all the cases reported, in which codliver oil produced improvement, had intestinal tuberculosis. With the exception of McConkey's study, the paucity of details in the reports prevents any critical analysis. For example, the article by Frimodt-Moller (8), describing excellent results in 25 cases, contains neither clinical nor pathological details and, according to the author himself, is premature. McConkey used the roentgen-ray as his sole criterion for the diagnosis of intestinal tuberculosis. In view of the fact that this method of diagnosis has been shown to be inaccurate in more than 50 per cent of cases (12), it is reasonable to assume that in many instances the diagnosis may have been incorrect. Furthermore, there are no necropsy findings given as definite proof of the diagnosis in any case. Incidentally one should note that, although in his final conclusions McConkey stated that 86 per cent of the cases treated with vitamines are alive as compared with 14 per cent of the untreated cases, he failed to appreciate the significance of the fact that his control cases had been ill in the hospital for a much longer time than the cases chosen for vitamine therapy. It may reasonably be suspected that his control cases were more seriously affected. Moreover his percentages are probably modified by the fact that his treated cases far outnumber the controls.

Our cases selected for treatment had, with one exception, frank or suggestive symptoms of intestinal tuberculosis. Some of them had presented clinical evidences of this condition for a long time before the vitamine therapy was instituted. However, these cases cannot be considered to have been in terminal stages, since two of them are still alive, a year after treatment was stopped, and three of the cases were under treatment 4 months, 10 months and 2 years, respectively, before autopsy revealed no evidences of healing.

CONCLUSIONS

1. The use of a high-vitamine diet appears to have been unsuccessful in the treatment of intestinal tuberculosis at the Montefiore Hospital.

2. Examination of the necropsy material of the cases studied clinically revealed little evidence of healing, and showed extensive fresh ulcerations despite prolonged treatment in several of the cases.

3. In our opinion, vitamine therapy is neither a cure for intestinal tuberculosis, nor a preventive of it.

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BRONCHIAL OBSTRUCTION AS A COMPLICATION OF PULMONARY TUBERCULOSIS UNDER ARTIFICIAL PNEUMOTHORAX

A Case Report[1]

WALTER I. WERNER

Occasionally tuberculous involvement of the mucosa of the larger bronchi occurs as a part of pulmonary tuberculosis. When this complication develops, symptoms and signs may be observed which cannot be satisfactorily explained by the results of physical examination. Clerf (1) has pointed out that bronchoscopic examination in tuberculosis is limited largely to those cases requiring special investigation. With the more general use of artificial pneumothorax in the treatment of pulmonary tuberculosis it is important that patients who develop obscure symptoms should be examined bronchoscopically. The object of this paper is to report a case of pulmonary tuberculosis that developed wheezing, blood-tinged sputum with fibrin, a choking sensation upon coughing, dyspnoea, cyanosis and suffocation while under treatment by artificial pneumothorax.

H. S.: 42 years old, white, single, female. Family and past history irrelevant. *Present illness:* In December, 1928, patient developed "influenza" from which she never fully recovered; has had slight cough with expectoration since that time. Sputum on admission contained tubercle bacilli. At time of entrance to sanatorium (December 26, 1929) had been under treatment for pulmonary tuberculosis for one year, and artificial pneumothorax had been induced on the right side eight months before admission. In June, 1930, developed periods of coughing, shortness of breath and sensation of choking. At times would expectorate gelatinous and blood-tinged, fibrinous plugs. These paroxysms were most marked at night when she assumed reclining position. General condition excellent. On examination all organs except the lungs were normal. Right hemithorax lagged. Tympanitic note elicited throughout the entire side. Tactile fremitus increased over back. Breath-sounds distant or absent throughout. No râles heard. No abnormal physical signs over left lung. X-ray showed approximately 60 per cent collapse and two shoe-string adhesions

[1] Pontiac, Michigan.

which held out the right apex. Left lung radiolucent throughout. *Laboratory data:* Many tubercle bacilli in sputum. Wassermann and Kahn reactions of blood negative. Blood count: haemoglobin 74 per cent, red blood cells 4,800,000, leucocytes 8,200. Differential count: polymorphonuclears 53 per cent, lymphocytes 33 per cent, large mononuclears 4 per cent. Urine normal.

Clinical course: Although only small refills of air (−2, −6; 200 cc., −2, +6) were given at 14-day intervals, dyspnoea and cough grew progressively worse. Because of marked feeling of tightness over right base and positive sputum, phrenicectomy performed, but produced no change in patient's condition. Attempts made to reëxpand right lung were unsuccessful. Fluoroscopic examination revealed the right lung remaining collapsed about 60 per cent. On evening of September 20, 1930, condition became critical. Dyspnoea was marked; there was cyanosis and suffocation and copious amounts of blood-tinged sputum were coughed up. Asthmatoid wheeze heard when one stood at the patient's side. A hurried physical examination of chest indicated percussion note hyperresonant over entire chest; amphoric breathing and scattered high-pitched rhonchi present over right side; movement of left hemithorax limited; breath-sounds bronchovesicular and harsh, but diminished over base; rhonchi noted posteriorly below 9th dorsal spine. These physical signs and symptoms led to the clinical impression of bronchial obstruction. On bronchoscopic examination, tracheal mucosa was found to be blood-tinged, covered with thick fibrinous exudate, and right main bronchus was collapsed. Left main bronchus almost completely occluded with thick fibrinous exudate, 500 cc. of which was aspirated from left bronchus. Respiration returned to normal almost immediately, and cyanosis disappeared. Large numbers of tubercle bacilli found in fibrinous secretion. Another bronchoscopic examination one week later showed that both right and left main-stem bronchi were partly occluded with granulation tissue which interfered with bronchial drainage. Sections of this granulation tissue were found to be tuberculous on microscopic study.

The pneumothorax has been discontinued, but it is still necessary to dilate right main-stem bronchus every four to six months. These subsequent bronchoscopic examinations show that trachea and left-stem bronchus are moderately inflamed but free from granulation tissue. Right main-stem bronchus is entirely closed, its orifice being partly replaced by strawberry-red mass covered by epithelium. Signs and symptoms of chronic bronchitis are present, and sputum still contains many tubercle bacilli. Right lung is completely reëxpanded, and roentgen studies reveal dense areas of fibrosis above 2nd rib.

DISCUSSION

The occurrence of dyspnoea in tuberculous patients under artificial pneumothorax is usually associated with (1) too large an amount of air,

(2) shifting mediastinum, (3) cardiac changes, (4) contralateral pleural effusion, (5) spontaneous pneumothorax, or (6) extensive spread of disease in the contralateral lung. Usually these changes may be determined by physical examination and the dyspnoea be accounted for. In the case reported, there was cough and dyspnoea with eventual symptoms of cyanosis and suffocation which could not be explained by any of these complications. The physical signs were suggestive of bronchial obstruction, and bronchoscopic examination revealed a tuberculous fibrinous bronchitis. Apparently this condition developed secondarily to the tuberculous parenchymal lesion, the bronchi being superficially infected by the discharges from the pulmonary foci. The progress of this disease was very slow, which explains the gradual development of symptoms. Coryllos (2) and others have called attention to atelectasis of the lung, both lobar and lobular, as a complication in the course of tuberculosis. In the case reported, there was no evidence, by physical signs, serial roentgenograms or studies of the intrapleural pressure, of atelectasis. The bronchial obstruction was not complete. A combination of factors were responsible for the later and more marked symptoms. The respiratory surface was decreased by the artificial pneumothorax and partial obstruction by granulation tissue of the right main-stem bronchus. Finally, the respiratory surface, already diminished, was further depleted by a sudden flooding with a serofibrinous exudate of the bronchi and left main-stem bronchus. This led to the symptoms of intense cyanosis, dyspnoea and suffocation.

It is probably fair to assume that the artificial pneumothorax played no part in the formation of the fibrinous casts, and that the association of the two conditions is a mere coincidence. A survey of the literature reveals only a few cases of fibrinous bronchitis, and none as a complication of artificial pneumothorax. Pagel and Henke (3) have shown that pulmonary tuberculosis is, more than any other disease of the lungs, accompanied by early and marked bronchial lesions. These lesions may be exudative, caseous or proliferative, and may lead to bronchial obstruction. Jackson (4) has reported instances, in which the entire lumen of the bronchus was occluded by cheesy pus and débris of a peribronchial lymph node which had eroded through. With this erosion of the peribronchial lymph node (into the bronchus) may be associated granulation tissue, usually of pale color, but occasionally reddish, and sometimes oozing blood.

SUMMARY

A case of pulmonary tuberculosis, under artificial pneumothorax, that developed cough, expectoration, wheezing respiration and dyspnoea of varying degree, is reported, and the bronchoscopic findings revealed a serofibrinous bronchitis of tuberculous nature with bronchial obstruction of the right main-stem bronchus.

I wish to express my thanks to Dr. William A. Hudson, and Drs. C. Hammond and W. Warren for the bronchoscopic data.

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PREGNANCY FOLLOWING EXTRAPLEURAL THORACOPLASTY

A Case Report

H. S. BOQUIST, J. H. SIMONS AND J. A. MYERS

Collapse therapy has restored large numbers of tuberculous patients to reasonably good health; so good in fact that many women whose tuberculosis was complicated by pregnancy have found it possible to go through pregnancy when the lung disease was brought under control by artificial pneumothorax. Moreover, subsequent pregnancies are reasonably safe as long as the lesion remains under control through this form of treatment. Phrenic exairesis and extrapleural thoracoplasty have also so restored the health of women that they have later gone through one or more pregnancies without reactivation of their tuberculous disease. The test of the value of our therapeutic measure is, of course, time. It is of more value from the prognostic standpoint to be able to report a case that has continued alive and well years after the surgical procedure than to report it immediately afterward. We desire to report the case of a young woman whose history of clinical tuberculosis dates from 1915, when she developed unilateral tuberculous cervical adenitis. Radical surgery was employed but the patient was not put on any tuberculosis regimen. In 1918 after a period of ill health she was found to have rather advanced tuberculosis of the left lung with cavity-formation. She was sent to Glen Lake Sanatorium, where, after a period of observation, artificial pneumothorax was instituted. She responded very well to this treatment and after a year left the institution. The lung was allowed to reëxpand. In the winter of 1920–1921, she had reactivation of the disease and the cavitation was more advanced. Numerous attempts at artificial pneumothorax failed to establish more than a small air-pocket in the pleural cavity because of many adhesions. Her sputum was positive; symptoms were present, such as loss of weight, cough, and occasional haemoptysis. Thoracoplasty seemed indicated but the operation was so new in this country that one or two surgeons refused to undertake the operation. She was then sent to the Glen Lake Sanatorium with the understanding that Dr. Arthur A. Law would consider extrapleural thoracoplasty. The first stage was performed in May, 1922, the second stage in September of the same year, and the third stage in September, 1923. She was discharged from the sana-

torium in March, 1924. In October, 1924, she started to work in a physician's office, where she remained until 1927. Soon after discontinuing work she was married, and on March 3, 1929, gave birth to a normal child.

The pregnancy was uneventful except for considerable nausea and vomiting during first three months and moderate dyspnoea during the last month.

Pelvic measurements revealed a justominor pelvis. The position at onset of labor was O.L.P. with moderate hydramnios.

The membranes ruptured before the onset of labor. Labor began immediately following this and was uneventful until the cervix was completely dilated and the head just below the spines, at which time the interval between the contractions was two to three minutes. The dyspnoea became extreme and the maternal pulse-rate was persistently high, 130 to 140. The foetal heart showed little recovery in rate between contractions, and it was thought advisable for the benefit of the mother and foetus to use midforceps. Due to the emergency and small size of the baby, the head was delivered in the posterior position with deep episiotomy. The duration of labor was four hours and twenty minutes. The baby responded immediately to resuscitation.

Puerperium uneventful.

With such a history it would be assumed that the patient would be extracautious. However, having emerged successfully from the experience of maternity, she supposed her life now could be lived on a normal basis and undertook to care for both household and child as a normal woman would. When the child was almost a year old the mother again began having symptoms of weakness, fever and cough. Her sputum became positive. Both she and the child were readmitted to Glen Lake Sanatorium. After another year, she was discharged and has had no recurrence of her trouble. The child is healthy and at no time has had a positive skin test.

The foregoing are the high lights of the case. The clinical records had its ups and downs, as all cases of advanced tuberculosis,—its periods of despair and renewed hope. It demonstrates that with our modern methods of collapse therapy a patient with far-advanced tuberculosis can be restored to what is practically normal living.

A DOUBLE-EXPOSURE ROENTGENOLOGICAL CHEST TECHNIQUE[1]

H. L. SAMPSON

Following extrapleural thoracoplasty (depending upon how extensive the operation is), there is a "falling in" of the chest-wall which in a great many instances is so pronounced that the diseased lung structure is difficult to see in the ordinary chest roentgenograms. The usual roentgen technique as pursued for differentiation of pulmonary structures is inadequate to register the tissue differentiation of the compressed lung. In the regular chest roentgenograms the diseased or compressed side appears as a more or less homogeneous density throughout. As a result of this, the structure of the compressed lung, to a certain extent, is lost sight of. Because of the irregular density as a result of the collapse, one feels less certain about interpreting intrapulmonary changes. The apparent degree of compression is not in all instances confirmed by the clinical or symptomatic "picture"; in other words, the lung appears well collapsed and no cavity-formation is visible on the usual chest roentgenogram,—yet the symptomatic picture is not in agreement. This has led us to adopt a variation in roentgen technique: namely (1) the usual technique for the better lung, and (2) a Potter-Bucky grid technique for the lung collapsed after thoracoplasty. It is a well-known fact that the use of the Potter-Bucky grid is advisable for tissue differentiation where the tissues are dense, such as may be the case with a severely diseased or collapsed lung. Ordinarily a Potter-Bucky grid technique is not satisfactory for pulmonary work, because the necessary exposure is too long; then, too, detail is sacrificed by too great an object, —film distance. However, as contrast is of vital importance in studying a compressed or airless lung, this Potter-Bucky grid procedure may be profitably used. With it one is able to "bring into view" cavity-formation that otherwise would be lost. The double technique is followed out on a single or a pair of stereoroentgenograms. In other words, only one pair of stereoroentgenograms is used to register both the aerated

[1] From the Roentgenological Department of the Trudeau Sanatorium, Trudeau Foundation, Trudeau, New York.

and the dense lung. In addition to the fact that both can be viewed on the one pair of films there is a distinct saving in expense. In our experience it has not taken the patient long or, for that matter, the physician, to dub the new technique, "'alf 'n 'alf," one-half of the film for the good lung and the other half for the diseased lung. Obviously this new procedure is reserved only for those cases in which one side is very dense; for example, thoracoplastic operation, pleurisy with effusion, thickened pleura, neoplasms, atelectasis or any other physiological or pathological process that replaces the normal, aerated lung with a dense shadow producing medium.

TECHNIQUE

One-half of each film is covered with a sheet of lead of sufficient thickness to ensure protection. The unprotected side is then exposed to register the "good" lung. The protecting lead is then shifted to the half of film which now has a registration of the "good" lung. The cassettes are then placed in either a horizontal or vertical Potter-Bucky grid apparatus. Care must be exercised in placing the patient in position, so that each shoulder is approximately the same distance from the top of the film. Then both halves of the chest will be symmetrically placed. To obtain proper perspective the cassette used with the tube in the high position for the good lung must again be used with the high tube position for the compressed lung. The exposure for the dense side will depend somewhat upon how great the density is. For heavy densities a spine technique is used, for lighter densities the exposure is shortened. Because there is little or no movement on the "diseased" side, reasonably long exposures (approximately five seconds) do not appear to be objectionable. However, the shorter the exposure, the less danger there is from blurring caused by motion. A small focal-spot radiator-type Coolidge tube is used to compensate for the short focal-spot film distance, which is to a great extent determined by the type of Potter-Bucky grid used. An average technique is as follows: Kv. variable; M.A. 10; distance 30 inches; time 5 seconds. The Kv. is varied for different depths of chests. The perspective on the Potter-Bucky grid side of the film is usually very satisfactory and one is able to evaluate the relative position of pulmonary and thoracic structures. However, too much reliance should not be placed upon it if further surgical procedure is contemplated, unless the surgeon and the roentgenologist can check the perspective by known anatomical landmarks. Up to the

FIG. 1A

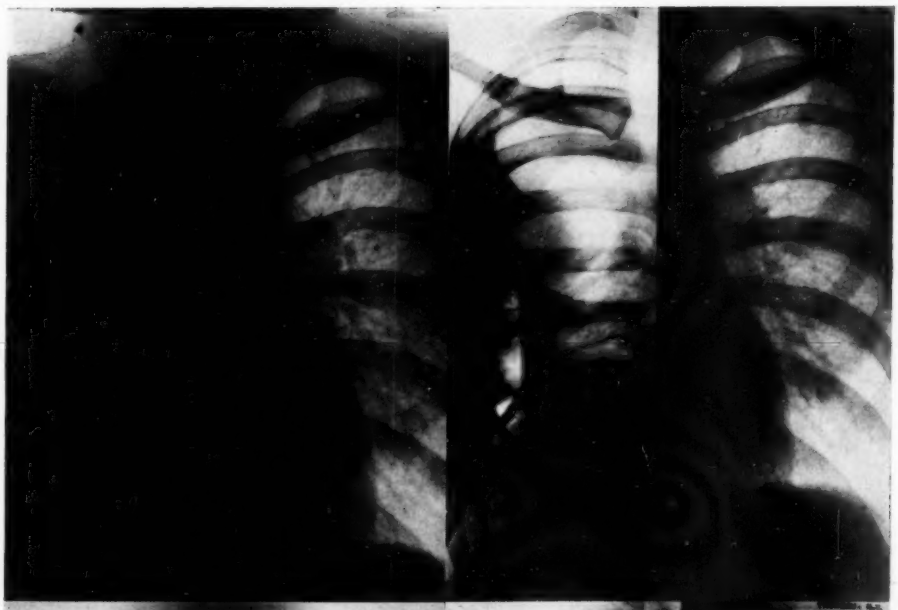

FIG. 1B

FIG. 2A

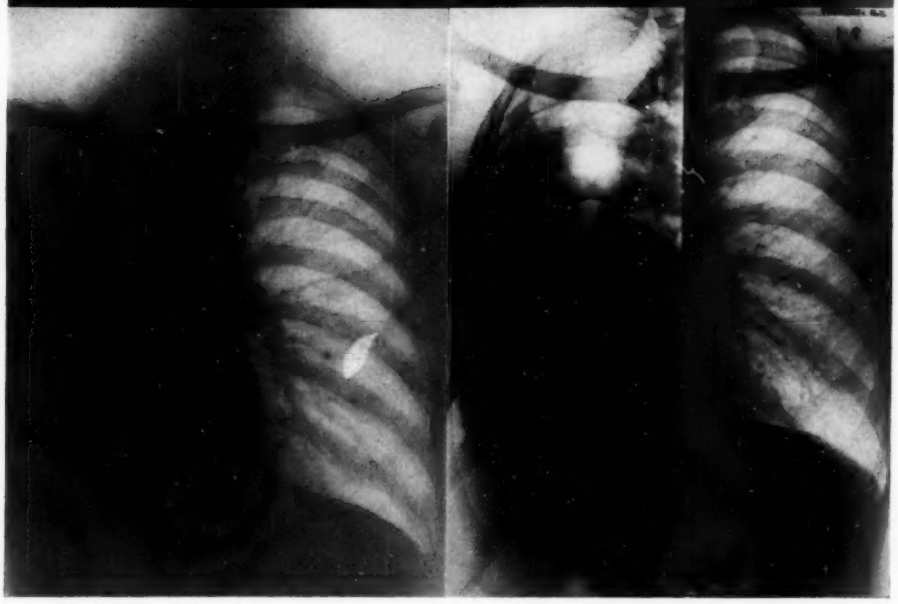

FIG. 2B

FIGS. 1A & 1B. Of a case of pyopneumothorax. The usual technique was used in 1A, with the result that the good lung is clearly visible whereas the diseased side is dense throughout.

Fig. 1B illustrates the value of the double technique. Small area of pneumothorax still remains with drainage tube *in situ*. Also, partially expanded lung is clearly visible.

FIGS. 2A & 2B. Illustrating the value of double technique. In 2A the left lung is clearly visible, whereas no conclusions can be drawn regarding the right lung because of the density of the shadow. The area of relative rarefaction in the upper third is the trachea drawn markedly to the right (see fig. 2B). Also, some conclusions can be drawn regarding the pulmonary process at the base.

present time we have not attempted to evaluate, statistically, the foregoing method. Suffice it to say that it has become a routine procedure when one side of the chest is dense and the opposite is amenable to the usual chest technique.

The writer is greatly indebted to Mr. Richard Walters for working out the details of the technique used.

COMPLEMENT FIXATION AS RELATED TO RESISTANCE AND ALLERGY IN EXPERIMENTAL TUBERCULOSIS

A. B. BAKER[1]

Within the past few years a great deal of experimental work has been done in an attempt to determine the protective values of BCG vaccination against tuberculosis (1, 2, 3, 4, 5, 6). Recently Clawson (6) reported experiments on the resistance against tuberculosis in rabbits vaccinated intravenously and subcutaneously with both living and heat-killed BCG. He discussed the relation of this resistance to the existing allergy as measured by the tuberculin test. In conjunction with this work it seemed warranted to make a serological study on a series of rabbits vaccinated with BCG in an attempt to determine whether there is any correlation between the concentration of the humoral antibody, measured by the complement-fixation test, and the degree of resistance or the allergy exhibited by the animals.

Of all the serological tests attempted in tuberculosis, complement fixation has received the most favor, although even its value, at the present time, is still disputed. Most of the work with the Bordet-Gengou reaction has been with the viewpoint of realizing a delicate diagnostic procedure capable of detecting certain early clinical cases of tuberculosis (7, 8, 9, 10, 11), and, still more important, to detect or determine the activity of such a lesion (12, 13). Little attention, however, has been given to the evaluation of the complement-fixation test as a measure of the relative resistance of the human body to a tuberculous infection and still less to the measure of the experimental protection in animals, especially those vaccinated with BCG. It is with this latter phase that we are principally concerned. Quite recently Hughes (14) reported a definite increase in the ability of rabbit's serum to promote phagocytosis of living tubercle bacilli, following repeated intracutaneous injections with heat-killed tubercle bacilli. This work, although using different procedures, is faintly confirmative of some of the results to be reported in this study.

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For this serological study 37 rabbits were used: 9 were injected subcutaneously with living BCG, 7 intravenously with living BCG, 7 subcutaneously with heat-killed BCG, and 9 intravenously with heat-killed BCG. There were 5 normal control animals. The rabbits were given 4 injections at weekly intervals of 1 mgm. of BCG, the tubercle bacilli being either living or heat-killed, depending upon the type of vaccination used. The different methods of vaccination and the reasons for using such methods have been discussed in an earlier publication (6).

The antigen used was prepared by forming a suspension of ground-up heat-killed tubercle bacilli. Of the numerous antigens reported in the literature (15, 16, 17, 18), this type is by far the most popular in this country. After running a series of comparative tests with variously prepared antigens, the method used was selected because it was fairly simple to prepare and gave the best results. The exact method of preparation was for the most part adopted from Miller (19). Twenty milligrams each of the BCG and the Ravenel bovine strains of tubercle bacilli were weighed out carefully in a centrifuge tube. A small amount of saline solution was added and the organisms killed by heating in a water-bath at 60°C. for half an hour. The saline solution was then pipetted off and to the 40 mgm. of organisms 180 mgm. of sodium chloride added; the entire mass was then ground with a glass rod to a fine paste for almost an hour. Distilled water was then added to make up to 20 cc., thus giving an isotonic solution. The suspension was then shaken thoroughly and allowed to stand for a few minutes so that the coarser particles settled out. This preparation was now ready for use, and could be kept for as long as at least four months in an ice-box without any appreciable deterioration, although occasionally it was necessary to regrind the coarser particles that had settled out. After numerous preliminary tests with both normal and tuberculous sera, it was found that 0.075 cc. of concentrated antigen, prepared as above, diluted with saline solution to a total volume of 0.25 cc., gave the most satisfactory results when used in testing the sera.

The blood in all the work was obtained by bleeding the animals from the heart. The serum, after its separation, was inactivated at 57°C. for half an hour. In order to measure the antibody titre, eight dilutions of each serum were used, starting with a 1:3 dilution and ending with 1:1,296 (table 1). In the first four tubes of each serum tested, the serum was diluted by a ratio of 1:3 in each tube. In the last four dilu-

tions, however, only a ratio of 1:2 was used, in order to prevent too rapid a jump in the dilution. Thus, the following eight dilutions were used for each serum: 1:3, 1:9, 1:27, 1:81, 1:162, 1:324, 1:648, and 1:1,296. Various dilutions of sera of a group of normal rabbits were tested, and the first dilution in which the controls showed no fixing of complement was adopted as the starting point in diluting the tuberculous sera. In this manner, no normal rabbits showed any significant fixation of complement, and the results obtained were, without doubt, due to the experimental inoculation employed.

The amboceptor, complement, and sheep cells were prepared in the rountine manner, as used for the ordinary complement-fixation test. We worked with a total volume of 1.25 cc., thus using 0.25 cc. of each of

TABLE 1

Representative protocol. On the extreme left the various dilutions of each serum used are shown. This table contains the relative readings in the four different groups of vaccinated animals condensed into a single protocol in order to facilitate the comparison

	CONTROL	NORMAL	SUBCUTANEOUSLY WITH LIVING *BCG*		INTRAVENOUS LIVING *BCG*		SUBCUTANEOUS HEAT-KILLED *BCG*		INTRAVENOUS HEAT-KILLED *BCG*	
1:3	−	+ −	++++	++++	++++	++++	++++	++++	++++	++++
1:9	−	− −	++++	++++	++++	++++	+++	++++	++++	++++
1:27	−	− −	++++	++++	++++	++++	+++	++	++++	++++
1:81	−	− −	++++	++++	++++	+++	++	−	++++	++++
1:162	−	− −	+++	++	++++	+++	+	−	++++	++++
1:324	−	− −	+++	++	+++	−	−	−	++++	++++
1:648	−	− −	++	+	+++	−	−	−	+++	++
1:1296	−	− −	−	−	−	−	−	−	++	−
NaCl	−	− −	−	−	−	−	−	−	−	−

the ingredients. The contents of each of the tubes were, therefore, as follows:

1: 0.25 cc. of $\frac{1}{3}$ dilution of the rabbit's serum to be tested, inactivated at 57° for 30 minutes.

2: 0.25 cc. of the tuberculous antigen, using 0.075 cc. concentrated antigen + 0.175 cc. saline solution.

3: 0.25 cc. of a $\frac{1}{15}$ dilution of guinea-pig serum (complement).

4: 0.25 cc. of 5 per cent sheep cells + 0.25 cc. of rabbit amboceptor (haemolytic system). (This is added after incubation.)

The foregoing material was uniform for every tube with the exception of the vaccinated rabbit's serum, which was diluted as described in a

previous paragraph. The tubes were then incubated for 75 to 90 minutes and the haemolytic system added. Following the addition of the haemolytic system, the tubes were again incubated for not more than half an hour and the test was read as plus (+), two-plus (++), three-plus (+++), and four-plus (++++). A four-plus test showed no haemolysis, while plus (+) showed almost complete haemolysis.

All the animals were tested for the first time three days after the third inoculation. Following the fourth injection, the rabbits were tested every other week until the antibody titre reached its peak, and then the sera examined but once each month until the titre had dropped to zero. A few weeks after the disappearance of the humoral antibody, the animals were again injected with a small dose of tubercle bacilli, and the sera tested in a few days in an attempt to determine whether the antibody had already been destroyed, or whether it had merely left the circulation and had attached itself to the tissue cells. Tuberculin tests were employed on every animal monthly to determine the degree of allergy and its relation to the complement titre.

In all this work the source of the sera was not known until after the test had been read. This procedure was introduced intentionally in order to get an unbiased reading, and thus avoid any influence that other experimental work might unconsciously exert upon the results.

RESULTS OF EXPERIMENTS

In all the four vaccinated groups, the antibody-titre curve was very similar, varying only in the height to which it rose (chart 1). The humoral antibody started to appear immediately and increased rapidly, reaching its peak by the 10th to the 17th day after the last inoculation. It remained at the peak until about the 30th day; then began to decrease gradually, so that by the 100th day the antibody, measured by the complement-fixation test, had completely disappeared from the circulation. As stated above, the antibody curve varied in the differently inoculated groups only in the height to which it rose. The highest titres were obtained in those rabbits vaccinated intravenously with heat-killed BCG, these reaching an average titre of 1:972. The rabbits vaccinated subcutaneously with living BCG, intravenously with living BCG, and subcutaneously with heat-killed BCG followed with average antibody titres, respectively, of 1:648, 1:621, and 1:117 (chart 1). None of the control animals demonstrated any specific tuberculous antibody. It is evident,

therefore, that the vaccination with BCG stimulated the production of a humoral antibody, and that the amount of antibody produced varied with the mode of vaccination.

Is there any relation between the antibody titre and the allergic phenomena as measured by the tuberculin test? In all the animals vaccinated subcutaneously with living BCG the Mantoux test became positive, varying from four-plus (necrotic centre) to two-plus. Even after the 100th day, when the humoral antibody had disappeared, the

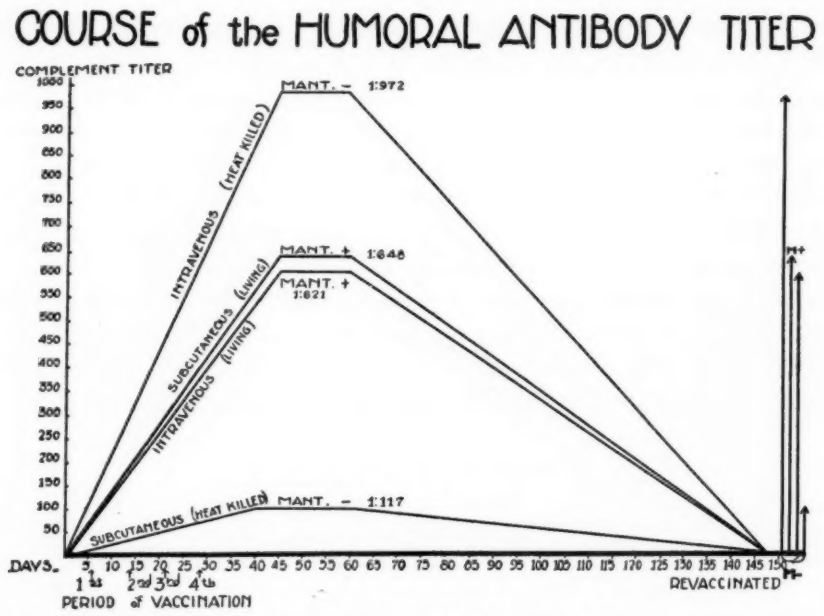

CHART 1. This chart shows the relative height of the antibody titre (measured by the complement fixation test) at each day of the experiment. The relative course is similar in each group of vaccinated animals, varying only in the height to which the humoral antibody rose.

skin test in these animals remained positive, indicating persistence of the allergy (chart 2). Only a little more than half of the rabbits vaccinated intravenously with living BCG manifested a positive skin test, while none of the rabbits vaccinated with heat-killed organisms (subcutaneously or intravenously) gave a positive tuberculin test in spite of the numerous times that the test was attempted (chart 2). These results are quite striking, especially if we focus our attention on the group of animals vaccinated intravenously with heat-killed organisms. It will

be remembered that these rabbits developed the highest complement titres (1:972), but none showed a positive skin test. If we can assume that the tuberculin test is a sufficiently sensitive test of tuberculous allergy, then we must conclude from the above results that different substances are at the basis of the allergic reaction and the complement-fixing ability of the animals' sera.

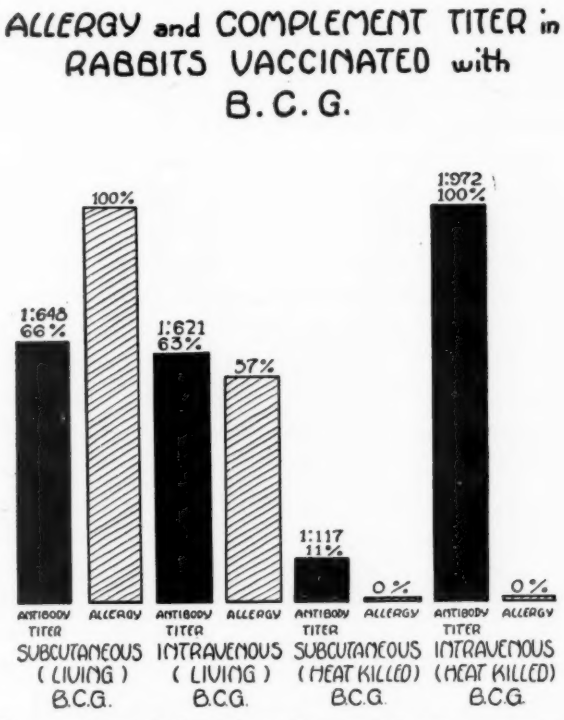

CHART 2 The percentage of allergy in each group is based on numerous repeated tests upon each animal, thus giving a sufficient number of skin tests in each group to make percentages significant. The percentages of the antibody titre were derived by adopting the group with the highest average titre (the animals vaccinated intravenously with heat-killed BCG having a titre of 1:972) as 100 per cent.

It seems fairly evident that the humoral antibody does not measure the allergy possessed by the animal. Does this antibody titre show any correlation to the resistance of the rabbits against tuberculosis? In experiments recently reported from this department (6), rabbits were vaccinated exactly as in our work and then injected with virulent bovine tubercle bacilli, in an attempt to determine the relative resistance of the

various groups to tuberculosis. All the vaccinated animals showed much greater resistance to tuberculosis than did the normal controls. However, of the vaccinated animals, those inoculated intravenously with heat-killed BCG and subcutaneously with living BCG showed by far the greatest protection, while the least protection was manifested by those animals vaccinated subcutaneously with heat-killed organisms. If we assume that a similar resistance was developed in the animals used for our study, then it appears that those animals developing the highest antibody titres also showed the greatest tuberculous resistance (intravenously with heat-killed and subcutaneously with living BCG), while those rabbits developing the lowest antibody titres also showed the least resistance to tuberculosis (subcutaneously with heat-killed BCG). It seems, therefore, that the humoral antibody might be a measure of the relative resistance developed in animals vaccinated with BCG.

The humoral antibody disappeared at the end of 100 days in all of the rabbits. The question arose: Had the antibody been destroyed or had it only left the circulation and attached itself to the cells, awaiting only a mild stimulus to drive it again into the circulation? Larson in 1919 (20) had emphasized the fact that humoral antibodies readily attach themselves to tissue cells but are easily driven out into the circulation by simple stimuli. He speaks of this as the exfoliative stimulus and uses it as an explanation for the apparently beneficial results from foreign-protein therapy. Duprez (21) established this fact in tuberculous patients.

In this work, all of the rabbits were revaccinated with a small dose of organisms at the end of 100 days (at which time the humoral antibody had entirely disappeared). The complement-fixation test was repeated on all of the animals a few days later, thus not allowing a sufficient lapse of time for actual development of new humoral antibodies. In confirmation of Larson and Duprez, we found that the titre had again risen in each group to its average level, indicating that the antibody had not been destroyed. More extensive work on this phase of the problem is now in progress on a large group of patients and will be published at some future date.

CONCLUSIONS

1. In experimental work with tuberculosis, vaccinated animals can be definitely differentiated from the nonvaccinated controls by the aid of the complement-fixation test.

2. The antibody titre in vaccinated animals does not measure the existing allergy, but does appear to parallel the resistance of the animals to experimentally produced tuberculosis.

3. The humoral antibody produced by vaccination is not destroyed when it cannot be detected by the complement-fixation test but leaves the circulation and can be exfoliated by various stimuli.

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FOLLOW-UP INFORMATION ON 2,031 TUBERCULOSIS PATIENTS ONE TO THIRTEEN YEARS AFTER DISCHARGE FROM SANATORIA[1]

G. J. WHERRETT

Thirteen years have elapsed since the first patient was discharged from the Sanatorium at Fort Qu'Appelle. Since that time the Saskatchewan Anti-Tuberculosis League, now operating sanatoria at Fort Qu'Appelle, Saskatoon and Prince Albert, has endeavored to keep in touch with all patients who have been discharged from its institutions. This has been done primarily to gather information that might be of value to future patients. This information, gleaned from the study of recoveries, relapses and deaths, is proving of utmost value in advising tuberculous people, and passing on to these something of the experience of others, so that they are better able to cope with their disease, their occupation and environment.

Invaluable information has also been obtained regarding diagnosis, prognosis, treatment and after-care, to say nothing of the wider field of prevention, by this study. Comparison may also be made with the results of other institutions (1), and the previous report submitted from Fort Qu'Appelle in 1925 (2). That report covered those treated between October 19, 1917, and December 31, 1924. This report embraces not only those included in the previous report but also those discharged up to December 31, 1929, and contains records of 2,031 patients.

It has seemed advisable that this study of the results of sanatorium treatment should be confined to those patients whose disease was definite, and, as experience widened, X-ray apparatus and technique improved, and laboratory facilities increased, revision of the information in all files has been made, and present day minimal standards of diagnosis applied. As a result, a number of patients formerly diagnosed as having tuberculosis have been excluded. This seemed necessary that the information gleaned might be accurate.

This report has been made up from information received from patients,

[1] From the Fort Qu'Appelle Sanatorium of the Saskatchewan Anti-Tuberculosis League, Fort San, Saskatchewan, Canada.

their friends, family physicians, health officers and nurses, the Department of Pensions and National Health, the Travelling Consultants of the League, and sanatorium review examinations. It is more than encouraging that the "Unheard From" group amounts to only 5.96 per cent, scattered as many of these patients are over this continent and even Europe. Sincere thanks are due to those who in any way submitted information which has been of value in determining the present state of health of this large number of discharged sanatorium patients.

1. FACTORS CONSIDERED TO HAVE A BEARING ON RESULTS

In order that conclusions recorded may be compared with those of other workers, factors considered to have had some bearing on results of treatment are here set out.

1: Nonselection of cases: The group of patients treated has been an unselected one representing all types of tuberculosis occurring in one of the prairie provinces of Canada inasmuch as there are no other institutions for the care of the tuberculous. Cases are admitted in all stages,—early, advanced and hopeless. In the opening years, following the practice which obtained in most institutions, an attempt was made to secure only hopeful cases. Study of the proportion of minimal and advanced cases even at that time shows, however, no variation from year to year, though there has been an increase in the percentage of early cases since treatment beds have been adequate, and the free treatment of tuberculosis was established in Saskatchewan in 1929. The tendency with the favorable minimal case in the early days of the League was toward a short period of treatment as financial reasons forced these patients to seek an early discharge and longer home treatment.

2: Racial immunity: While racial origin is a factor which has some bearing on immunity and consequently upon the results of treatment, the number of Hebrews, Indians and half-breeds treated is so small as to have very little effect on the general results of treatment.

3: Length of treatment: Length of stay in the Sanatorium, other things being equal, is a factor which should have a very direct relation to the permanence of results obtained. This we consider due not only to the better condition of the patient on discharge, but also to the more ade-

quate education and experience which the patient secures by remaining for a longer time. Broadly speaking, there was a gradual increase from five to twelve months in the period of treatment from 1917 to 1925. Since then it has fluctuated around twelve months, the average being 10.1 months. Table 1 gives the average length of stay year by year, set off against the number of relapses and readmissions.

4: Age, sex and marital state: It was noted that 76.83 per cent of those patients discharged were in the age-group, 15–40, while only 11 per cent were under 15 years, and 12.17 per cent over 40 years. In comparison with the 1925 report it was noted that there is very little change in the

TABLE 1

Length of treatment in relation to relapses and readmissions

YEAR	TOTAL DISCHARGED ALIVE	MONTHS		RELAPSES	PER CENT	READMISSIONS
		Total	Average			
1918	86	427	4.96	21	24.41	41
1919	158	719	4.55	39	24.68	54
1920	201	1,200	5.97	49	24.37	55
1921	173	1,421	8.21	29	16.76	59
1922	148	1,098	7.41	19	12.83	37
1923	147	1,395	9.48	18	12.24	48
1924	116	1,312	11.31	10	8.62	31
1925	166	2,718	16.37	8	4.81	42
1926	190	1,849	9.73	6	3.15	35
1927	173	2,048	11.83	10	5.78	37
1928	204	2,829	13.86	9	4.41	60
1929	269	3,317	12.33	7	2.6	68
	2,031	20,333	10.01	225	11.07	572, or 28.16%

age-group percentage. It was thought when the previous report was made that the small percentage of children was due to the excess of young adult males who were war casualities which enlarged the number in that group. Although returned soldier patients are at present reduced to a minimum, these figures still hold. The smaller percentage of patients over forty is consistent with the age-groups of our population and with the curve of the tuberculosis death-rate in Saskatchewan, which shows only a relatively small number of tuberculosis deaths after middle life. This rarity of breakdowns after middle life in an agricultural community such as Saskatchewan is in contrast to the greater number of breakdowns that occur in industrialized communities.

There is a considerable increase in the number of female patients. There were 1,087 males of which 381 were married and 706 single, as against 944 females, 450 of whom were married and 494 single.

5: Condition on admission: This has been found to have a very definite bearing on the results of treatment. The proportion of acute and chronic types has remained fairly constant during this period of years, and has varied around 3.6 per cent acute and 96.4 per cent chronic. The percentage of nonpulmonary cases has increased from 5.72 to 14.82 per cent. The proportion of bacillary, nonbacillary and nonpulmonary cases is shown in table 4.

2. A STUDY OF RECOVERIES

A study of recoveries shows that, out of 2,519 tuberculous patients, 488, or 19.37 per cent, died in the Sanatorium upon first admission. As the period of treatment was prolonged, and as all classes of patients were admitted without selection, the proportion who died in the Sanatorium during their first period of treatment has increased from 15 to 27 and now fluctuates around 25 per cent.

The after-results of sanatorium treatment are shown by a study of the remaining 2,031 tuberculous patients. It is the prognosis of this latter group that is of special interest to tuberculosis workers and to all others who are interested in the expectancy of life of tuberculous persons who have received sanatorium treatment.

Accordingly, from follow-up reports these have been classified according to their present condition, and, specifically, according to their ability to work and the presence or absence of symptoms. An analysis of tables 2 and 3 will show that the group "Well and Working" corresponds more or less with the combined groups "Apparently Cured," "Apparently Arrested," and "Arrested."

Stage of disease on admission: Conclusions made in the last report have been further borne out by this study (table 4). Among 291 pulmonary cases discharged who were admitted as "Minimal" the number who are now working is 219, or 75.25 per cent. Among 1,439 pulmonary cases, admitted *in the advanced stage of the disease, 574, or 39.88 per cent, are now working.* As regards failures to respond to treatment, of those admitted in the "Minimal" stage, 29, or 9.9 per cent, are now dead, while

TABLE 2

Follow-up year by year in relation to ability to work and symptoms

YEAR OF DISCHARGE	TOTAL DISCHARGED ALIVE	WELL AND WORKING		SYMPTOMS AND LIGHT WORK		UNABLE TO WORK		DIED		UNHEARD FROM		DIED IN SANATORIUM NUMBER	GRAND TOTAL OF DISCHARGES	PERCENTAGE OF GRAND TOTAL DIED IN SANATORIUM	PERCENTAGE OF GRAND TOTAL OF DEATHS
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent				
1918	86	41	47.67	3	3.49	7	8.14	30	34.89	5	5.81	3	89	4.44	37.77
1919	158	64	40.50	11	6.97	4	2.53	69	43.68	10	6.32	20	178	15.05	52.15
1920	201	65	32.33	9	4.48	15	7.47	104	51.74	8	3.98	30	231	14.83	58.90
1921	173	54	31.21	11	6.36	15	8.68	83	47.97	10	5.78	23	196	12.18	54.36
1922	148	46	31.09	9	6.09	11	7.43	65	43.91	17	11.48	23	171	15.48	52.56
1923	147	55	37.42	4	2.72	13	8.84	64	43.54	11	7.48	36	183	19.67	54.70
1924	116	43	37.07	9	7.76	8	6.90	49	42.24	7	6.03	42	158	27.04	57.86
1925	166	65	39.15	16	9.65	22	13.25	57	34.34	6	2.61	48	214	25.56	51.12
1926	190	85	44.74	20	10.53	13	6.84	62	32.63	10	5.26	49	239	21.81	47.32
1927	173	78	45.09	16	9.25	34	19.65	35	20.23	10	5.78	59	232	27.31	42.02
1928	204	86	42.15	31	15.20	43	21.08	29	14.22	15	7.35	62	266	25.24	36.00
1929	269	102	37.88	65	24.20	68	25.28	22	8.18	12	4.46	93	362	27.88	33.78
Total...	2,031	784	38.60	204	10.05	253	12.45	669	32.94	121	5.96	488	2,519	19.37	45.93

TABLE 3

Follow-up year by year in relation to present condition

YEAR OF DISCHARGE	TOTAL DISCHARGED ALIVE	APPARENTLY CURED		ARRESTED		APPARENTLY ARRESTED		QUIESCENT		IMPROVED		UNIMPROVED		DIED		UNHEARD FROM		DIED IN SANATORIUM. NUMBER	GRAND TOTAL OF DISCHARGES
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent		
1918	86	30	34.88	6	6.98	5	5.81	6	6.98	2	2.33	2	2.33	30	34.88	5	5.81	3	89
1919	158	49	31.02	12	7.60	7	4.43	8	5.06	2	1.26	1	0.63	69	43.67	10	6.33	20	178
1920	201	45	22.39	18	8.95	2	1.00	11	5.48	4	1.99	9	4.47	104	51.74	8	3.98	30	231
1921	173	31	17.92	14	8.10	8	4.62	14	8.10	5	2.89	8	4.62	83	47.97	10	5.78	23	196
1922	148	26	17.56	16	10.82	2	1.35	13	8.78	4	2.70	5	3.38	65	43.92	17	11.49	23	171
1923	147	23	15.65	27	18.37	4	2.72	9	6.12	—	—	9	6.12	64	43.54	11	7.48	36	183
1924	116	21	18.11	16	13.97	7	6.03	10	8.62	3	2.59	3	2.59	49	42.24	7	6.03	42	158
1925	166	15	9.04	23	13.86	19	11.45	26	15.66	6	3.61	14	8.43	57	34.34	6	3.61	48	214
1926	190	16	8.42	43	22.63	20	10.53	26	13.68	8	4.21	5	2.63	62	32.63	10	5.27	49	239
1927	173	7	4.05	41	23.70	24	13.87	28	16.18	9	5.20	19	10.99	35	20.23	10	5.78	59	232
1928	204	5	2.45	36	17.65	32	15.69	49	24.02	23	11.27	15	7.35	29	14.22	15	7.35	62	266
1929	269	1	0.37	31	11.53	60	22.30	85	31.60	34	12.64	24	8.92	22	8.18	12	4.46	93	362
Total...	2,031	269	13.24	283	13.93	190	9.35	285	14.33	100	4.92	114	5.12	669	32.94	121	5.96	488	2,519

TABLE 4

Stages and results of 2,031 patients after an average period of 1–13 years after discharge

CLASSIFICATION ON ADMISSION	TOTAL DISCHARGED ALIVE		WELL AND WORKING		SYMPTOMS AND LIGHT WORK		UNABLE TO WORK		DIED		UNHEARD FROM		DIED IN SANATORIUM		GRAND TOTAL OF DISCHARGES
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	
Clinical															
Minimal	253	12.46	167	66.00	26	10.28	23	9.09	24	9.49	13	5.14	0	0	253
Moderately advanced	358	17.63	204	56.98	47	13.13	23	6.43	53	14.80	31	8.66	9	2.45	367
Far advanced	224	11.03	91	40.63	24	10.72	25	11.16	68	30.35	16	7.14	34	13.18	258
Bacillary															
Minimal	38	1.87	24	63.16	2	5.26	3	7.89	5	13.16	4	10.53	0	0	38
Moderately advanced	153	7.53	48	31.38	20	13.07	23	15.03	58	37.89	4	2.63	6	3.77	159
Far advanced	704	34.66	80	11.36	60	8.52	124	17.62	422	59.94	18	2.56	406	36.58	1,110
Nonpulmonary	301	14.82	170	56.48	25	8.30	32	10.63	39	12.96	35	11.63	33	9.88	334
Total	2,031	100.00	784	38.60	204	10.04	253	12.46	669	32.94	121	5.96	488	19.33	2,519

Forty-seven deaths from nontuberculous causes: 43 after discharge, and 4 in sanatorium on first admission.

of those admitted in the "Advanced" stage 601, or 41.96 per cent, are now dead.

In separating the clinical from the bacillary cases it was found that of those admitted in the same stage of the disease there were three times as many clinical as bacillary cases that are well and working.

This further bears out the opinion that has long been held that minimal disease is curable, that the possibility of cure becomes less as the disease advances, and that clinical cases have a better prognosis than those in which bacilli are found in the sputum.

3. STUDY OF MORTALITY FROM DATE OF ADMISSION

Of the 2,519 tuberculosis patients treated more than 31 days and discharged prior to December 31, 1929, 1,157, or 45.93 per cent, are now dead (of all causes). Of this number 47 died of a nontuberculous cause, making the tuberculosis deaths 1,110, or 44.06 per cent. Four hundred and eighty-four, or 43.60 per cent, of the total deaths died in the Sanatorium during their first period of treatment and an additional 626, or 56.40 per cent, of the total deaths have died of tuberculosis since their first discharge.

A study was also made of the relation of condition on admission to mortality.

Of the 1,043 who died from pulmonary tuberculosis, only 16, or 1.44 per cent, were admitted to the Sanatorium in the "Incipient" stage, and 109, or 9.83 per cent, in the "Moderately Advanced" stage, while 918, or 83.70 per cent, were admitted in the "Far Advanced" stage, and 67, or 6.03 per cent, were nonpulmonary. Furthermore, among the 1,043 pulmonary cases that are dead, 158, or 15.15 per cent, were clinical cases on admission; 885, or 84.85 per cent, were bacillary. Of the 334 nonpulmonary cases 67, or 20.06 per cent, have died of tuberculosis.

4. STUDY OF MORTALITY FROM DATE OF DISCHARGE

Table 2 shows the percentage who have died since returning home, according to year of discharge. Six hundred and sixty-nine, or 32.93 per cent, of the 2,031, are dead of all causes, and 626, or 30.82 per cent, have died of tuberculosis.

Table 4 shows the number who have died since discharge according to their stage of disease. Of the minimal cases only 9.9 per cent are dead, of the moderately advanced group 21.06 per cent are dead, while of

the far-advanced group 52.80 per cent are dead. The nonpulmonary group shows 12.32 per cent dead.

Heise and Hennegar, reporting on *Condition in 1931 of Patients discharged from the Trudeau Sanatorium from 1916–1930*, gave the following figures of deaths after 15 years according to classification: "Minimal 4.1 per cent, Moderately Advanced 15.9 per cent and Far Advanced 49.6 per cent."

The 1926 follow-up report from the Saskatchewan Anti-Tuberculosis League gave the following deaths according to classification on admission: "Minimal 4.91 per cent, Moderately Advanced 11.07 per cent, Far Advanced 49.14 per cent."

It is of importance for physicians, and others, who are endeavoring to cope with the problem of tuberculosis, to know what the expectancy of life is in the case of patients who fail to recover after discharge.

The deaths in the various years after discharge were as follows: First year, 30.77 per cent; second year, 20.92 per cent; third year, 15.33 per cent; fourth year, 8.15 per cent; fifth year, 4.15 per cent; sixth year, 4.32 per cent; seventh year, 2.88 per cent; eighth year, 1.60 per cent; ninth year, 1.60 per cent; tenth year, 0.96 per cent; eleventh year, 0.16 per cent; twelfth year, 0.16 per cent. Seventy per cent, in other words, died during the first three years. After the sixth year the average is 0.2 per cent or less than the average mortality from tuberculosis for Saskatchewan.

5. STUDY OF RELAPSES

As it is important that relapses be prevented or reduced to a minimum, a study of relapses has again been made. A relapse has been interpreted as a second breakdown giving rise to symptoms requiring further treatment, either in or outside a sanatorium. The better the condition of the patient on discharge the less has been the tendency to relapse, though occasionally relapses have occurred in cases in which the disease was "Apparently Arrested" and even "Apparently Cured." Of the 2,031 patients who returned home 206, or 10.04 per cent, relapsed. The percentages of relapses during the first six years of the operation of the Sanatoria were much higher than during subsequent years. As the average length of sanatorium treatment increased to approximately one year (see table 1) there was a definite drop in the percentage of relapses which has since been maintained. In other words, when insufficient

treatment is given the percentage of relapses is in inverse ratio to the length of treatment. A study of the cause of relapse, adopting the same classification as in the 1925 report, shows the number of relapses in which the following causes had a definite bearing: Insufficient treatment originally 40, overwork 59, unexplainable 29, unhygienic living conditions 21, unhygienic working conditions 2, indiscretions in recreations or morals 20, intercurrent disease 23, concurrent disease 9, operative procedure 2, unknown 18, mental factor 1. Under the heading "Unexplainable" are listed those in which everything seemed favorable, yet they relapsed. Those listed under "Cause Unknown" are those in which no information was available as to exact cause of relapse.

1: Relapse in relation to occupation: When we consider the males alone, we see that there is a slight increase in the relapses among those engaged in outdoor occupations. This is not because they were working outdoors, but because outdoor work in an agricultural province means farming and other manual labor of a heavy character. The majority of male patients who broke down due to overwork were those undertaking outdoor work. More supervision is necessary of this group to prevent relapses.

2: Relapse in relation to condition on admission: A study was also made of relapses in relation to the condition of patients on admission.

From this study it was found that the higher percentage of relapses occurred among patients in the incipient and moderately advanced stages, and that the percentage of relapses among the clinical cases was greater than among the bacillary cases.

It must be taken into consideration that many of the advanced cases became progressively worse and never recovered sufficiently to relapse. Among those are found not the relapses but the deaths. In the second place, the patients who had germs in their sputum realized to a greater extent the need of treatment, and, as a result, coöperated better. Finally, the greater proportion of relapses among the clinical cases is to some extent due to their having improved quickly after admission and having returned home too soon. Unlike the bacillary cases they did not take the necessary precautions after discharge and relapse was the inevitable result.

Even after relapse the early cases returned to the Sanatorium in better condition than the majority of patients, and the result of their second

period of treatment was better than the average result obtained by all classes.

Out of a total of 2,031 patients discharged alive, there were 225 relapses, or 11 per cent. These are summarized as follows:

			per cent
Clinical:	Minimal	29	12
	Moderately advanced	56	24.89
	Far advanced	39	17.33
Bacillary:	Minimal	4	1.78
	Moderately advanced	35	15.55
	Far advanced	40	17.78
Nonpulmonary		22	9.78
Total		225	100

3: Relapse in relation to age and sex: A study was made of the sex and age in relation to relapse, and it was found that, of the 1,087 males who returned home, 140, or 12.87 per cent, relapsed. Of the 944 females, 66, or 6.99 per cent, relapsed. In this group the percentage of relapses among the males was considerably greater than among the females. This is probably due to the fact that, as far as the single women are concerned, their occupation and living conditions were more sheltered than in the case of the males. Generally speaking, relapses increase with age, reaching the average at twenty. After twenty-five the incidence is more than three times that under twenty-five, the peak being in the age-period, 40–44.

4: Relapse in relation to pregnancy and child-bearing: From information obtained from the report one feels that the last word has not been said regarding the unfavorable effect of pregnancy and child-bearing in relation to tuberculosis. The idea which is all too prevalent, that tuberculous people are prolific, is not borne out by the facts; particularly is it the case since contraceptive teaching has not been given in this group, at least not by the Sanatoria. Only 85 pregnancies occurred among 944 females. The French dictum that "A tuberculous woman bears one child usually, two seldom, and three never," is not borne out by this study.

Opinions expressed at the June meeting of the Section of Obstetrics and Gynaecology of the Royal Society of Medicine combined with the Tuberculosis Association on January 16, 1931, are of interest and certainly not in accord. Mr. Alex Bourne stated that after twelve years' experience of infirmary work his general impression was that

pregnant women should be informed that pregnancy was of no consequence when the disease was not apparently active, that it was unfortunate when the disease was active, and that it was disastrous when the disease was advanced. In general, it could be said that abortion had no place in the treatment of pregnancy when associated with phthisis. Lactation during the puerperium must be disallowed, and whenever possible the infant removed from probable infection by the mother (3).

From the experience of tuberculosis and pregnancy to date our opinion might be here stated that only in the advanced active case does pregnancy seem to have a deleterious effect: that the pregnancy should not be terminated except in this group and then not after the first three months. Sanatorium care of the mother before and after confinement is advisable. The child should not be allowed to suckle and should be separated from the mother. The course of labor has not been long or unduly severe in cases that have been on prolonged bed-rest. There is even some justification for the belief that pregnancy in certain cases has a beneficial effect on the course of the disease, particularly with sanatorium care of the mother before and after confinement and preventorium care of the baby. Lactation, care of the baby, loss of sleep and domestic worries dependent on the birth would seem to have a more adverse effect on the course of the disease than the pregnancy itself.

The following figures are of interest:

	Mothers	*Children born*	*Number of Deaths of Mothers*	*Percentage*
Bacillary	21	28	7	33.3
Non bacillary	58	98	5	8.6
Nonpulmonary	6	14	0	0

5: Relapse in relation to the length of time since discharge: From the standpoint of prognosis as affecting relapse, time as a factor of safety appears to be of utmost importance. This fact should be kept in mind by all engaged in the treatment of tuberculosis.

Relapses during various years occurred as follows: First year 34.67 per cent, second 16 per cent, third 20 per cent, fourth 10.22 per cent, fifth 4.44 per cent, sixth 6.22 per cent, seventh 1.78 per cent, eighth 2.67 per cent, ninth 1.33 per cent, tenth 1.33 per cent, eleventh 0.89 per cent, twelfth 0.45 per cent.

PROBLEM OF AFTER-CARE

This problem, an important one in tuberculosis, deserves some comment in regard to what it means to Saskatchewan, and what, if any, are

the remedies. The total number not working but able to do so, and this includes those whose disease is quiescent or better, amounts to only 27. In order that these might not be said to be affected by economic conditions, and affecting only certain years, it is to be noted that these are found almost evenly distributed among the discharges of each year. In an agricultural Province such as Saskatchewan after-employment does not constitute a major problem such as it does in more highly industrialized communities or countries, and is one which, because of its small size, is not impossible of being solved. The next report may throw further light on the subject.

CONCLUSION

Some 2,031 patients have been followed from one to thirteen years after discharge; only 5.96 per cent are not heard from. Factors considered to have a bearing on results are enumerated. A study of recoveries, deaths, and relapses has been made in relation to age, sex, stage of disease on admission, length of treatment, time since discharge, and effect of pregnancy and childbirth.

Prolonged and uncertain as the treatment of tuberculosis must necessarily be, results are nevertheless encouraging and the outlook optimistic. The fact that 49 per cent of our patients have returned to work is ample justification for the existence of the Sanatorium. It must also be borne in mind that sanatorium treatment is applying the principle of isolation in respect to a communicable disease and the follow-up of patients has laid the foundation for the intensive preventive programme now being carried out among families and contacts. These facts are a source of satisfaction and pride to all who are privileged to play a part in the sanatorium movement.

Thanks are due to Dr. R. G. Ferguson who prepared the 1925 report and under whose direction and advice the present work was undertaken. To Miss S. G. MacKinnon, R.N., special thanks are due for her painstaking work in obtaining information, working out details, and preparing the accompanying tables, without which this report would have been impossible.

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A STATISTICAL STUDY OF TUBERCULOSIS CLINICS IN GRAYS HARBOR COUNTY, WASHINGTON[1]

HOWARD L. HULL[2]

The following represents a brief statistical study of tuberculosis clinics held in Grays Harbor County in the State of Washington. It includes a summary of 2,769 cases over the period from September 1, 1926, to August 31, 1933. The aims of this study are (1) to convey an idea of the number of persons reporting to "chest clinics" in a large, rather sparsely settled county who presumably have tuberculosis and the larger number who have nontuberculous conditions; (2) to describe conditions which have to be met where clinics are held in remote places and without facilities or the assistants of the large city clinics; and (3) to summarize the important symptoms which bring the patient to the clinic.

Grays Harbor County is located in Southwestern Washington. Its western boundary is the Pacific Ocean. Its area is 1,869 square miles, which is larger than that of the State of Rhode Island and only slightly smaller than the State of Delaware. The population at the last census was approximately 65,000, though at present one would believe that it is closer to 60,000 or less. The nationalities range from the native-born white American to the native Indian, Scandinavian, Finnish, German and Slavic. The Negro and Oriental races are very much in the minority. The Scandinavian and Finnish are probably next to the native American in number.

Climate: The climate is remarkably equable the year round. The temperature is seldom below freezing except for short periods of time and rarely as high as 85 degrees. The annual average temperature is 45.2. The precipitation is very high, as the average for the year is 85 inches, and during the year, 1932, it exceeded 110 inches.

Forests of evergreens, especially Douglas fir, cedar, spruce and hemlock abound. In Grays Harbor County is situated part of the Olympic forest which is considered to be America's last wilderness of virgin timber of unbelievable density and growth.

[1] From Oakhurst Sanatorium, Elma, Washington.

[2] Yakima, Washington.

In reference to occupations, the logging industry attracts a large number of laborers, many of whom are unskilled. Logging is subject to many interruptions incident to the needs of the lumber mills. This creates a great deal of unemployment in the periods when the logging camps are not operating, and the same is true, likewise, in regard to the lumber mills when an oversupply of their finished product is at hand. Sanitary conditions in the logging camps are in many instances poor. The workers sleep in bunk-houses, often in double-deck bunks, under conditions of poor ventilation and overcrowding. It is not hard to imagine that a person suffering with tuberculosis could easily infect his fellow-workers under the conditions we have seen in these camps. As the supply of labor is usually far beyond the demand, there is no particular incentive to employers to improve the men's working conditions, and to look after their comfort in hours of leisure. It is a noteworthy fact, however, that the workers in logging camps are well-fed and the quality of the food is good.

Injuries to the chest, received in working in the woods or in the factories, do figure to a certain extent in cases of traumatic tuberculosis.

Organization: The tuberculosis clinic work in Grays Harbor County is handled as a part of the county sanatorium program, being classified as "Field Service." A Tuberculosis Fund is raised by taxation and by money received by the sanatorium from patients admitted who are able to pay something toward their care, and also by the state subsidy. The law provides that the state shall pay $5.00 per week for each patient in the sanatorium who does not pay for his full cost of maintenance. A portion of this fund is allotted to clinic work.

The clinics are arranged by the County Nurse, who gives her entire time to the work but who is not on the sanatorium staff. The nurse does the field-work, which includes finding the cases and referring them to the clinic; carrying out as far as possible any orders given relative to each patient; the follow-up work, which consists of arranging for such reëxaminations as are needed; and visiting the patient's home to give nursing advice and supervise home care.

The clinics which form the basis for this study are held three times a week. The first clinic of the week is for reëxaminations of patients discharged from the sanatorium and this by special appointment. The second clinic is for new cases or for reëxamination of out-patients. These two clinics are held at the sanatorium. The third clinic is held in some

distant part of the county. Those held about the county in the first two weeks of each month are in the two large centres of population, namely, Aberdeen and Hoquiam; the other clinics are at smaller places previously arranged by the county nurse. School-houses and community centres are utilized for the clinics held in the remoter parts of the county.

The equipment carried consists of portable scales, a rule for measuring height, outing-flannel capes for covering the chest, the various statistical blanks, clinical thermometers, tongue blades, and the stethoscope. In the last three years, two dilutions of Old Tuberculin, 1 to 1000 and 1 to 10,000, have been carried with sterilized needles and hypodermic syringes for performing the intracutaneous test. Much difficulty has been encountered in regard to this test, the principal trouble being the securing of accurate reports on the results. It is impracticable for the clinic physician to visit a remote place in 48 hours and read the result of the test, and frequently the patient does not report to the nurse for her to determine the result. Sometimes it is necessary to have the patient write a brief description of the reaction of the test but this is rarely satisfactory; hence, it not infrequently happens that the tests are made but no result is ascertained. In the past two years, special clinics have been held at schools in which intracutaneous testing was the sole object, another trip being made to the school two days later to read the results of the tests and arrange for X-rays to be taken at the sanatorium in the case of those who react positively. In this work financial restrictions have limited the number of X-rays taken. Hence, only a beginning has been made in this direction and no statistics of this phase of the work are given in this study, as they are too meagre to justify conclusions.

In each instance in which the patient is raising sputum a suitable container in a mailing-case is given for him to mail a specimen to the state laboratory so that a report may be sent later to the examiner.

The clinics have been restricted to residents of Grays Harbor County.

Procedure: In the early days of the clinics any person who presented himself was examined. This was done to encourage persons who suspected that they might have tuberculosis to come to the clinic and be examined. It was soon found, however, that the number presenting themselves was so large that it was impossible to give even a superficial examination. Likewise, patients presented themselves with conditions in no way related to tuberculosis, and thus consumed time which rightfully should have been spent in examining other cases. In order to pre-

vent this, examinations were restricted to patients referred by their attending physician, and those referred by the County Nurse, or by a social agency. In spite of this, at the present time patients coming from some distant part of the county often present themselves for examination. If the nurse decides, in interviewing them, that tuberculosis is a possibility, a history is taken and they are given the benefit of an examination. As the financial depression deepened more nontuberculous cases sought the aid of the clinic.

The coöperation of the medical profession has been most important, and has been splendidly given to this clinic work. One reason, we believe, is that a physician's reference is usually sought and preferred before making the examination; also, whenever a patient is referred by a physician, a letter is written to him giving a brief summary of the examination and our recommendations. If the patient has no physician, an effort is made to send him to some competent doctor near him. Further, it is distinctly understood that these patients are examined for diagnosis only. No treatment is given, so that they must always be referred to a physician or dentist, as the case may be, for treatment that seems indicated. This has avoided the criticism that the general public is being pauperized, and it has enlisted the coöperation and support of the regular medical profession. We may also add that an effort is made to get the patient away from irregular practitioners and cults and from incompetent dentists, especially of the advertising type.

At every examination made, the patient is told enough about the findings so that he will understand what should be done. The details of the examination or of the findings are later sent to the medical attendant. Enough is told the patient at the time so that he should feel that his visit has had some educational value. Leaflets on tuberculosis are given him. It has not been practicable, except in rare instances, to give talks to clinic patients on tuberculosis, but, where clinics are held at schools, they have usually been followed by a short talk to the pupils and their parents on the general subject of tuberculosis. The county nurse on her home visit is expected to go into details regarding prophylaxis in the case of each tuberculous patient discovered, and to arrange for examination of the contacts.

System followed in clinics: The patient is taken in the order in which he comes to the clinic. No preference is given, out of fairness to those who come early. No special appointments are given at the clinics. The

nurse takes the patient's history on duplicate (carbon-copy) statistical clinic blanks on which various questions may be answered by plus or zero, leaving blank a space for the examiner to make special notes. The nurse retains the carbon-copy. The history is on one side of the blank, and the examination on the other side. When the history has been taken, the patient is weighed and measured, his average weight for height and age recorded, and his temperature and pulse recorded. He is then brought before the examiner, stripped to the waist, the chest covered only with an outing-flannel cape. The examiner notes the history taken and adds certain notes under the subject of "Present Complaints," and usually confirms certain of the answers to important questions on the blank. The examination is then made in a routine manner, paying particular attention to the teeth and throat in addition to the chest examination.

Owing to the large number of persons presenting themselves for examination, it is recognized that only very essential methods of physical diagnosis can be used. Special stress is laid on a careful history. A tentative diagnosis is made upon the impression the examiner gets from his physical examination and the history. A tentative diagnosis only can be justified in the short time that can be taken for each examination. To counteract the just criticism of too rapid work that is thus necessitated, every patient who is considered a suspect is asked to have an X-ray taken, either at a nearby hospital or at the sanatorium, and to return for another examination, being told a definite date to report. The County Nurse is expected to do the follow-up work on such cases, but many such persons are never seen again, as they may belong to the itinerant-laborer class that disappears without leaving an address. Patients in whom a diagnosis of tuberculosis seems justified at the clinic examination are advised then and there to sign an application blank for admission to the sanatorium, if they are eligible for admission by having resided in the county for one year. Right here is one of the serious difficulties of our system which we believe is quite common in other clinics—the fact that a large waiting list for the sanatorium must be maintained, especially for men, because by the nature of our population, by far the larger number of applicants are men.

Under "tentative diagnosis" on our blanks to be filled out, "non-T.B." signifies that nothing justifies the diagnosis of tuberculosis. "Prob. non-T.B." means that tuberculosis is unlikely but must still be excluded by

further study. "Prob. T.B." means the condition is tuberculous until proved otherwise. "Suspic." means a strong suspicion of tuberculosis and, in the mind of the examiner, is half-way between "Probably tuberculous" and "Probably non-tuberculous." If pulmonary tuberculosis is diagnosed an effort is made at the clinic to classify it in more detail according to the scheme of the National Tuberculosis Association. So-called "hilum" tuberculosis can, of course, not be definitely determined at one clinic examination.

In the statistical summary to follow, the large number of nontuberculous cases will be noted. In each instance an effort was made to suspect the cause of the symptoms, then tell the patient the suspected diagnosis and refer him to the physician (or dentist) who was believed especially qualified to treat the condition. Where "focal infection" has been noted, it was done upon what appeared to be some obvious condition, but seldom did we get a chance to obtain confirmatory reports.

Surgical tuberculosis was excluded from clinics except where the major disability was pulmonary.

STATISTICS AND COMMENTS

Total number of clinics held	field	265
	sanatorium	619
		884

Total original (first examinations)	2,769
Total reëxaminations	3,352
Total examinations	6,121

While almost three times as many clinics were held at the sanatorium, by far the greater number attended the field clinics.

Age, sex and social condition

Age groups		*Sex*		*Social Condition*	
Under 15 years	796	Male	1,339	Married	1,053
15–20	332	Female	1,430	Single	1,569
20–30	695		2,769	Widowed	57
30–40	497			Separated or divorced	90
40–50	252				2,769
Over 50	197				
	2,769				

The adolescent group predominated, with 1,128 under the age of 20 years, amounting to 40.7 per cent. The sexes were almost evenly divided, and considerably more single than married patients applied to the clinics.

Source of reference

Publicity	1,023
Nurse or social agency	450
Physician	1,296
	2,769

By "Publicity" is meant that the patients came to a clinic by the advice of friends or because they saw notices of the clinics in local papers. Of the patients, 1,296, or 43 per cent, were referred by their physicians, about three times as many as were referred by the nurse.

Tentative diagnosis

Tuberculosis	563	or	20.4 per cent
Probably tuberculosis	131	or	4.7 per cent
Suspicious of tuberculosis	280	or	10.1 per cent
Probably nontuberculous	535	or	19.3 per cent
Nontuberculous	1,260	or	45.5 per cent

Only one-fifth of all cases examined justified a tentative diagnosis of tuberculosis (usually pulmonary). Combining the probably tuberculous and the suspicious, there were 411 cases, or 14.8 per cent, that were likely to be tuberculous, and required further study. All such patients were given appointments for reëxamination and where it was practicable to secure reports an intracutaneous test was made to be followed by X-ray if the result was positive. In 1,795, or 65.8 per cent, tuberculosis was considered unlikely.

Tuberculosis (563 cases)

Pulmonary Tuberculosis:

Active	Minimal (including "hilum")	49
	M. A.	114
	F. A.	257
Quiescent	Minimal	1
	M. A.	3
	F. A.	5
Apparently arrested	Minimal	3
	M. A.	2
	F. A.	7
Arrested	Minimal	3
	M. A.	3
	F. A.	4

Apparently cured	None
Tuberculous peritonitis	9
Pleurisy: acute	47
Pleurisy: chronic	25
Tuberculous osteitis	7
Tuberculous adenitis, active	20
Tuberculous adenitis, inactive	3
Renal tuberculosis	1
Total	563

Of 563 cases, 31 of the pulmonary type were believed to be in various stages of inactivity. The so-called "hilum" type has been included in "minimal." (The few "hilum" cases found were determined by later X-ray.) Attention is called to the very small number of cases of lymph-node tuberculosis;—only 23, or 4 per cent. This may be accounted for in part by the pure-milk campaign carried out by extensive tuberculin testing of cattle and the elimination of the reactors. The one case of renal tuberculosis had been diagnosed by a urologist and was sent to the clinic to determine if pulmonary disease existed. Only 72 cases of pleurisy, or 12.7 per cent, were diagnosed. These were considered tuberculous in origin on account of the history or in connection with other findings. In most of the acute cases an effusion was present. An extra effort was made to get an X-ray in these cases.

With few exceptions the cases of tuberculous peritonitis were admitted to the sanatorium for observation and treatment. A number of these had been discovered accidentally at operation in a general hospital.

Among the active pulmonary cases one notes that, of the 420 cases, 257, or 60 per cent, were far advanced and only 49, or 10 per cent, were minimal. This largely agrees with the findings of other observers who deplore the fact that in spite of the continuous educational campaign the early cases do not commonly come to the clinics. In the present investigation it only emphasizes the necessity for more nurses to find the cases and supervise them.

NONTUBERCULOUS CASES

In 1,260 cases a tentative diagnosis of tuberculosis seemed unjustifiable. In such cases when some other diagnosis suggested itself, if it seemed highly likely, it was recorded on the clinic blank. In 432 cases the following tentative diagnoses were made:

Thyroid gland disease	66	Bronchial asthma	33
Heart disease	99	Empyema	8
Bronchitis (acute and chronic)	124	Malnutrition	1
Bronchiectasis	44	Conjunctivitis	1
Bronchopneumonia	33	Influenza	1
Pulmonary abscess	12	Abdominal carcinoma	1
Pneumonitis (chronic)	9	Total	432

The predominance of bronchitis,—124 cases, or 28.7 per cent,—is not surprising. The grouped pulmonary conditions (excluding bronchial

asthma) amounted to 222 cases, or 51.3 per cent, and would naturally bring the patient to the chest clinic. Thyroid and heart disease amounting to 165 cases, or 38 per cent, because of their accompanying fatigue and dyspnoea, probably caused the patient to suspect that he might have tuberculosis. In the case of heart disease not a few had haemoptysis as the suspicious symptom.

In the single case diagnosed as conjunctivitis a phlyctenular variety was suspected but not proved.

FOCAL INFECTIONS

Focal infections in the tuberculous or nontuberculous were noted where they seemed obvious. Confirmations of such diagnoses were rarely received. No doubt careful examinations by a dentist or rhinologist would have revealed far more than we reported, yet, on the other hand, they might have failed to find as many such infections as we suspected.

Focal infections	Teeth (including gums)	323	
	Tonsils	344	
	Sinuses	248	
		915	or 33 per cent

No search for foci of infection elsewhere in the body was made. Frequently observed, especially in nontuberculous cases, was the apparently important relation between focal infections and chest pains, subacute and chronic bronchitis and bronchiectasis.

CHIEF COMPLAINTS

The clinic records have been reviewed to determine the chief complaint in each case, that is, what brought the patient to the clinic. In some instances there were several outstanding complaints, so that it was difficult to decide which one to consider. Some of these chief complaints are ridiculous for one coming to a tuberculosis clinic and rather suggest an excuse for a free examination than a suspicion of tuberculosis in the mind of the patient; as, for example, deafness, dysmenorrhoea, dizzy, and no complaint. In most instances these complaints, recorded below in order of frequency, are in the language of the patient.

Summary of Chief Complaints in Order of Frequency

Pains (618)		Cough	433
Abdomen	50	No complaints	406
Back	36	Fatigue	298
Chest	520	Colds	239
Hip	6	Bronchial trouble	7
Leg	6	Choking feeling	6
Underweight	107	Diarrhoea	6
Haemoptysis	79	Slow in school	5
Lymph nodes, enlarged	64	Dizzy	5
Loss of weight	64	Feet, swelling of	5
Nervousness	62	Palpitation of heart	3
Dyspnoea	54	Catarrh	3
Fever	53	Earache	2
Asthma	42	Painful menstruation	2
Headache	39	Overweight	2
Sore throat	24	Anaemic	1
Stomach trouble	23	Hay-fever	1
"Flu"	22	Deafness	1
Sputum	20	Hives	1
Pleurisy	20	Rheumatism	1
Night-sweats	14	Skin eruption	1
Hoarseness	10	Total	2,769
Adenoids	9		
Chest injury	9		
Appetite, loss of	8		

COMMENTS

Pain was the chief symptom which brought 618 patients (22.3 per cent) to the clinic and 84 per cent of this number had pain in the chest. Next in frequency (15.6 per cent) was cough. It is strange that so common a symptom did not rank first but strangest of all is that "no complaints" figured next in 406, or 14.6 per cent. In many such cases this was due to the fact that the subject was a contact case. Fatigue in only 298 cases (10.7 per cent) ranked considerably lower in importance than one would think.

Eight of the most common chief complaints and pleurisy (of which only 20 complained) were then checked through the records to determine the tentative diagnosis made in each case. The results in the table on the following page speak for themselves.

Only about a third of those whose chief complaints were chest pains or cough or colds had tuberculosis. In fatigue and pleurisy the percentage is higher and it is very high in haemoptysis. Underweight does not figure high in a tentative diagnosis of tuberculosis. It is a surprise that 20 per cent having no complaints should have tuberculosis.

*Principal Chief Complaints and Tentative Diagnosis Made**

CHIEF COMPLAINT	NUMBER OF CASES	NON-TUBERCULOUS per cent	TUBERCULOUS per cent
Chest pains	520	335–64	185–36
Cough	433	290–67	143–33
No complaints	406	326–80	80–20
Fatigue	298	155–52	143–48
Colds	239	150–63	89–37
Underweight	107	83–78	24–22
Haemoptysis	79	25–30	54–70
Lymph nodes	64	30–47	34–53
Pleurisy	20	10–50	10–50

* Per cent is based in each instance on the number of cases of that particular complaint.

SUMMARY

1. A study has been made of 2,769 cases reporting at 884 chest clinics held in a thinly populated county of Western Washington (Grays Harbor County) over a period of seven years.

2. The mode of conducting the clinics and the limited facilities as well as handicaps to the work have been described.

3. Statistics have been tabulated in reference to age, sex, social condition and diagnosis.

4. A study of chief complaints has been carried out to find out their relation to the tentative diagnosis made.

CONCLUSIONS

1. A tentative diagnosis of tuberculosis was made in 563, or 20.4 per cent. The disease was more or less suspected in 411, or 14.8 per cent, and unlikely in 1,795, or 65.8 per cent.

2. Only 10 per cent of the tuberculous were in the minimal stage. Sixty per cent were far advanced. Of nontuberculous conditions more than half were bronchitis.

3. Focal infections were widely prevalent and were considered a factor in one-third of all cases. They are a likely cause of chest pains in a large number who report to clinics.

4. Pain was the commonest symptom (22 per cent) which brought the patient to the clinic and especially pain in the chest (84 per cent of those who had pain); cough was next (15.6 per cent), but only about one-third of those having these chief complaints probably had tuberculosis. Twenty per cent of those who reported "no complaints" had tuberculosis.

The appreciation of the writer is hereby expressed to the nurses and secretary of Oakhurst Sanatorium for the preparation of the statistics and the typing of this report.

A SURVEY OF ARTIFICIAL PNEUMOTHORAX IN REPRESENTATIVE AMERICAN TUBERCULOSIS SANATORIA, 1915–1930[1]

With Special Attention to the Question of Termination of Treatment and Later Results

ANDREW PETERS, ALTON S. POPE, WILLIAM H. MORRISS, EDWARD N. PACKARD AND OSCAR O. MILLER

INTRODUCTION

There has long been a need for more precise and comprehensive data bearing on the matter of therapeutic pneumothorax, as well as other forms of collapse therapy, in the treatment of pulmonary tuberculosis. Such a study should cover an extended period, both on account of the usual chronic course of tuberculosis and because of the difficulty of evaluating the comparative results of any therapeutic measure without the lapse of sufficient time. Especially does this desideratum apply when we consider the eventual condition of the lung after discontinuance of pneumothorax and its relation to the patient's life, function and well-being. Again, it is desirable to include material not from one, nor even several, but from many sources, in order to reduce to a minimum the elements of personal temperament, prejudice, and difference in methods of collecting, recording and estimating data. At the same time, such methods must be sufficiently uniform or comparable to permit grouping them together for final analysis.

With the foregoing considerations in view, the *Committeee on Artificial Pneumothorax of the American Sanatorium Association* was appointed early in 1929 by the former Chairman of the Clinical Research Committee, Dr. J. Burns Amberson, Jr., and has continued its labors, being reappointed from time to time by the President or Executive Committee. At its inception special interest was expressed in the subject of the termination of pneumothorax therapy, the optimum time to allow this, and the results to be expected, particularly the late or "end" results. There was also much interest, at times amounting to controversy, as to

[1] Based on studies and reports of the Committee on Artificial Pneumothorax of the American Sanatorium Association, 1930–1933.

the extent of the indications for this mode of therapy and as to how far it has been or is being pursued in our American sanatoria.

In this particular study we have attempted (1) to bring our knowledge. more to date, (2) to make it more truly composite, and (3) in some respects to amplify and differentiate. To obtain sufficient data to warrant the extensive analysis comtemplated, resort was had to the questionnaire method. We cannot but agree with Riviere that, in such a disease as phthisis, no matter needs more cautious and judicious handling than the statistical results of any mode of treatment. There are some quite obvious disadvantages in this method and, if indiscriminately and undiscriminatingly applied, it may well result in confusion and gross errors, misinterpretation of data and mistaken conclusions. On the other hand, if used discriminatingly, with a working familiarity with its pitfalls and the data carefully analyzed, much valuable information can be gained which would be very difficult for one or several men otherwise to acquire. We do not assume infallibility in the method of collecting or handling the data on which this survey is based, but we have devoted a great deal of forethought to the best ways of eliciting the significant facts, and one of the members of our committee has had the benefit of special training in statistical analysis.

DETAILED METHOD OF SURVEY

About the end of 1929 a preliminary form letter was sent to 183 members of the American Sanatorium Association, mostly heads of tuberculosis institutions, explaining our purposes and asking them if they wished to be included in our study. Responses to this preliminary query were received from 67 members, of whom 50 manifested a desire to collaborate. The greater part of our data were eventually derived from institutions in New York, Massachusetts, Connecticut, Michigan, Minnesota, California and the Dominion of Canada, but there were enough scattered returns from other places to be distinctly worth while.

We next sent a detailed questionnaire to the 50 men or institutions above referred to. This questionnaire was divided into two parts, the first containing general questions designed to ascertain in what proportion of patients, over the period mentioned (1915–1930) or over the period of existence of the institutions (if opened later than 1915), pneumothorax therapy had been attempted or carried on; also, the proportion of so-called "operative failures" and other related information of value. (See facsimile of questionnaire.)

The second part contained blank forms and headings for individual case records. This second detailed questionnaire was sent out toward the end of 1930 and returns were received up to the spring of 1931. Some data were eventually received from 24 of the 50 sources queried, but a number of them were incomplete or indefinite, or not so set forth so as to be readily analyzed. The total number of case-records suitable for statistical analysis was not so large as might have been expected, but this circumstance may have been attributable to our rather exacting criteria and to the existence of a number of gaps or absence of essential detailed information.

CRITIQUE OF METHODS EMPLOYED

We have already discussed the possible shortcomings of the questionnaire method and the means of avoiding most of them. Of course, ultimately, the value of the data supplied in a questionnaire will depend on the care and conscientiousness with which it is filled out. Aside from the individuals responsible for the data, most of whom we believe are careful and reliable, the points we have selected for precise information are such that, in most instances, the information either is, or is not, available and there is little room for vagueness.

It may be objected that our survey extends too far back and includes a period in which pneumothorax therapy was still in its infancy; that its technique has altered; and that methods then used are now obsolete. Pneumothorax therapy was certainly not as well established in 1915 as it is to-day, but it was being employed by a few competent sanatorium physicians at least as far back as 1910. (Trudeau, one of the first patients to be treated in this country, received his first inflations in 1910.)

Its technique had not been perfected and controlled in 1915 to the degree that it is to-day, but the fundamental principles were the same and it had certainly passed its experimental stage. If more practitioners would read and take to heart the best pneumothorax literature of the last two decades or more, we would see less often the same old mistakes of the past repeated again and again, just as the same old economic errors are repeatedly arising under new guises. Massive insufflations and inadequate duration of collapse were not confined to the so-called "historic period" of pneumothorax therapy. Admitting some differences in the technique of pneumothorax therapy between the earlier and later parts of the fifteen-year period selected, the number of cases included in the latter part, that is, from 1922 or 1923 on, were so much more numerous

that they would tend to minimize the effect of these differences on the tabulated results. We have been particularly desirous of having at least a moderate interval elapse since the termination of treatment before attempting to analyze end-results because of the protracted course of tuberculosis in general and the common tendency to exaggerate or be misled by temporary or apparent ameliorations,—the common and age-long pitfall of attempts to appraise methods of treatment of phthisis or pulmonary tuberculosis.

The possible criticism that our material is ill-assorted and of questionable reliability we have already dealt with in part. We do not believe that it is ill-assorted, except in the sense that the indications for pneumothorax therapy have doubtless differed with different men and institutions at the same time and with the same men and institutions at different times. This is to be expected and, in covering a wide enough field, is of advantage rather than the reverse.

DEFINITION OF TERMS

The detailed data in the second part of our study relate entirely to terminated pneumothorax cases. The term, *reëxpansion* or *reëxpanded lungs*, was first used; but it was later largely discarded as being a misnomer and inaccurate, since many patients in whom pneumothorax treatment is discontinued never actually have much reëxpansion of the collapsed lung. This is generally due less to the treatment than to the disease, a point often not properly grasped.

It was further necessary to adopt criteria to be used in our summaries and tabulations. Among these were: *1:* What constitutes pneumothorax treatment? *2:* What are the criteria of what we chose to call *effective collapse*? *3:* How to define such a term as *symptom-free* or *not symptom-free*? We first thought of using the term *sick* for the latter, as simpler and shorter, but it is a less accurate term, especially when applied to tuberculosis. Terms such as *termination of pneumothorax intentional*, or the reverse, and patient *living* or *dead*, are, of course, self-explanatory. A little more difficulty arose when we came to *sputum positive* or *negative*. It would be advisable to make these terms conform to those in the latest classification system of the National Tuberculosis Association, but these specifications have been altered from time to time. When we come to such matters as the extent and amount of involvement, either infiltration or cavitation, we should like to be precise; but we finally decided that for our purposes the physicians' estimates would be more

valuable and certainly more readily obtainable than a classification based on exact measurements. Not only would these be unobtainable in very many cases but, perhaps, even unreliable or misleading; for example, a superficial cavity of moderately large roentgenographic diameter may be much less serious than a smaller and deeper one in which drainage is poor and badly located topographically. We have, therefore, left some latitude here.

1: Effective collapse: This term, which we have frequently employed, requires careful definition, and here we have combined clinical, roentgenographic and laboratory criteria. We decided that these three conditions should be met, or at least two of them, when the third was doubtful or not stated:

1: Disappearance of symptoms
2: Disappearance of bacillary sputum
3: Demonstrable closure of cavities, especially roentgenographically.

2: Termination of pneumothorax intentional or unintentional: Intentional termination is to be assumed when refills have been allowed to lapse, and termination is *unintentional* when obliterative adhesions have encroached on the pleural cavity. Some question may arise in the case of pleuritic exudates, but, here again, it is necessary to rely on individual judgment. Cases discontinued because of other serious complications outside the chest should probably come under the *intentional group*, although we do not definitely specify this.

3: Definition of pneumothorax treatment: For purposes of this analysis we required that (1) there must be a demonstrable pleural space, and (2) the patient must receive at least 100 cc. of air or gas at regular intervals over a period of at least three months.

SUPPLEMENTARY OR SUBSEQUENT PROCEDURES

Naturally a certain number of patients included in our analyses had been subjected also to other procedures and collapse measures, such as phrenicectomy and thoracoplasty, and in a few cases apicolysis or thoracotomy-drainage of empyemata. The major surgical procedures came generally at a later date. We finally decided not to consider any of these separately: first, because they constituted a small minority and insufficient numbers to warrant detailed analysis, and, second, because information bearing on these procedures was too limited.

SPECIFIC INFORMATION SOUGHT

The data sought in Part I of the questionnaire were the following:

1: The proportion of patients in whom pneumothorax treatment has been (a) attempted, and (b) carried out, in a group of representative American and Canadian tuberculosis sanatoria during the period 1915–1930.
2: The proportion of unsuccessful attempts, or so-called "operative failures," in such a group.
3: The proportion of cases so unsatisfactory as not to be worth consideration as treated cases, or discontinued within three months.

The second part of the problem deals with the results following termination of pneumothorax therapy. The method of correlation, well recognized in statistical analysis, has been used, and, in a few instances, multiple correlations have been necessary. We could have wished for more ample material, but believe that a careful compilation and analysis of this relatively small group is of much more value than a superficial and hasty analysis of a larger number. The following factors and relationships have been selected for investigation:

1: Results of treatment in cases in which termination of pneumothorax was (a) intentional or (b) unintentional.
2: Presence or absence of bacillary sputum in cases in which termination of pneumothorax was (a) intentional or (b) unintentional.
3: Relation of results of treatment to condition of treated lung before pneumothorax.
4: Relation of bacillary sputum at termination of treatment to condition of treated lung before pneumothorax.
5: Relation of bacillary sputum at termination of treatment to duration of collapse.
6: Relation of bacillary sputum at termination of treatment to condition of contralateral lung before pneumothorax.
7: Late results and fatality of pneumothorax-treated patients: relation to interval elapsed.
8: Late results and fatality in relation to (a) effectiveness of collapse and (b) involvement of contralateral lung.
9: Ability to work after treatment in relation to (a) effectiveness of collapse and (b) involvement of contralateral lung.
10: Late symptomatic results in relation to bacillary sputum at termination of treatment.
11: Late symptomatic results in relation to alterations in physical signs after termination of pneumothorax.

12: (a) Mortality in relation to duration of pneumothorax, and (b) duration of pneumothorax in relation to effectiveness of collapse.
13: Mortality in relation to condition of contralateral lung before pneumothorax.
14: Mortality in relation to bacillary sputum at termination of treatment.
15: Mortality in relation to effectiveness of collapse.
16: Effectiveness of collapse in relation to age of patient.
17: Symptomatic results in relation to age of patient.
18: Mortality in relation to age of patient.

Many other problems which might profitably be included in a study of pneumothorax will at once occur to the reader. We have necessarily limited the scope of this paper to the consideration of such questions as might reasonably be answered by the type of data available from our questionnaire and for whose solution our information seemed adequate.

SUMMARY OF GENERAL DATA ON THERAPEUTIC PNEUMOTHORAX

(*Derived from Part I of Committee Questionnaire*)

1: Proportion of admitted patients in whom induction of pneumothorax was attempted: The figures on the general incidence of pneumothorax in the sanatoria answering our questions differ somewhat according to whether we include cases with slightly inadequate data which cover pneumothorax treatment as applied among approximately 56,569 patients admitted over our fifteen-year period, or whether we restrict ourselves to those with fairly detailed, and hence more accurate, data which reduces the total of patients considered to 30,263. Based on the larger figure this is 8.8 per cent and on the restricted, 9.6 per cent of all patients. The figures vary between 0.45 per cent and 34 per cent with a usual range between 5 and 20 per cent.

2: Proportion of operative failures (*unsuccessful attempts*): This has been quite difficult to ascertain and we are by no means sure of the accuracy of the figures; in fact, we are quite sure they are too low. Based on the more restricted figures there were 14.4 per cent unsuccessful attempts; on the larger group, 17.6 per cent.

SUMMARY OF MATERIAL USED FOR DETAILED STUDY

From the total data submitted in the detailed case-reports, a sample form of which is shown, 396 cases were finally selected as having sufficiently complete information to warrant analysis. Of these, 132 were

males and 264 were females, a ratio of exactly 1 to 2. The reactions of the males and females to pneumothorax were so closely identical in regard to fatality and in all other respects that it did not seem desirable to separate them for the purposes of this report. The material finally included was received from 18 tuberculosis sanatoria or hospitals in widely separated parts of the United States and Canada; and, we believe, represents a good cross-section of what has been accomplished among the better type of institutions in the fifteen-year period referred to. Individual case records and data were received from the following institutions:

Arequipa Sanatorium, San Francisco, California (Dr. Ethel D. Owen)
Detroit Tuberculosis Sanatorium, Detroit, Michigan (Dr. Willard B. Howes)
Farm Sanatorium, Oklahoma City, Oklahoma (Dr. L. J. Moorman)
Gaylord Farm Sanatorium, Wallingford, Connecticut (Dr. William H. Morriss)
Glen Lake Sanatorium, Oak Terrace, Minnesota (Dr. P. M. Mattill)
Hamilton County Tuberculosis Sanatorium, Cincinnati, Ohio (Dr. Vera V. Norton)
Jordan Memorial Sanatorium, Riverglade, N. B., Canada (Dr. R. J. Collins)
Metropolitan Life Insurance Company Sanatorium, Mt. McGregor, New York (Dr. William H. Ordway)
Maybury Sanatorium, Northville, Michigan (Dr. Bruce Douglas)
Nopeming Sanatorium, Nopeming, St. Louis County, Minnesota (Dr. A. T. Laird and staff)
Norwich State Sanatorium, Norwich, Connecticut (Dr. Hugh Campbell)
New Jersey State Sanatorium, Glen Gardner, New Jersey (Dr. Samuel B. English)
Rhode Island State Sanatorium, Wallum Lake, Rhode Island (Dr. Harry L. Barnes)
Rutland State Sanatorium, Rutland, Massachusetts (Drs. E. B. Emerson, P. Dufault and staff)
Trudeau Sanatorium, Trudeau, New York (Drs. Fred H. Heise and J. Rosenblatt)
Summit Park Sanatorium, Pomona, Rockland County, New York (Dr. William J. Ryan)
S. W. Bowne Hospital, Poughkeepsie, New York (Dr. H. St. John Williams)
U. S. Soldiers' Home, Johnson City, Tennessee (Dr. Carl B. Neves)
Waverley Hills Sanatorium, Jefferson County, Kentucky (Dr. Oscar O. Miller)
William Wirt Winchester Hospital, West Haven, Connecticut (Dr. Willard B. Soper)

Individual Patient's Record, No. .....

1. Name of Institution .....
2. Re-expansion intentional (1) .....
   " unintentional (2) .....
   because of:
   (a) Progression in contralateral lung: .....
   (b) Pleural complications .....
   (c) Patient removed from treatment .....
3. Re-expansion established within first year of treatment (1).....
   " " " second " " " (2).....
   " " " third " " " (3).....
   " " after " " " " (4).....
4. Condition of treated lung before pneumothorax:
   Cavitation considerable (1).....
   Disseminated (a).....
   Localized (b).....
   " moderate (2).....
   Little or no cavitation (3).....
   Pneumonic consolidation (4).....
5. Condition of contralateral lung before treatment.
   No infiltration (1).....
   Little " (2).....
   Moderate " (3).....
   Infiltration with slight cavitation (4).....
6. Type of treatment
   Pneumothorax alone (1).....
   Pneumothorax and phrenicotomy (2).....

Results of Treatment at its Termination.

7. Symptom free (1).....
   Able to work (2).....
   Part time (a).....
   Full time (b).....
8. Sputum positive (1).....
   " negative (2).....
9. Estimate of lung function (on re-expansion)
   good or fair (1).....
   limited or none (2).....
10. Roentgen changes
    Cavities closed (1).....
    Consolidation resolved (2).....
    Absorption or clearing (3).....
    Fibrosis and slight contraction (4).....
    Pachypleuritis (5).....
    Marked shrinkage and visceral distortion (6).....
    Progression (7).....
11. Alterations in physical signs
    Râles diminished or disappeared (1).....
    " increased (2).....
    Cavity signs diminished or disappeared (3).....
    " " extended (4).....

Later Results.

	1–2 YEARS	2–3 YEARS	MORE THAN 3 YEARS	PERIOD ELAPSED AT FINAL CHECK-UP
12. Living				
(1) Symptom free				
(2) Able to work				
(a) Part time				
(b) Full time				
(3) Relapsed				
(4) Sputum positive				
(5) " negative				
(6) Cavitation reopened				
(7) Thoracoplasty done				
13. Dead.				

SAMPLE FORM OF QUESTIONNAIRE. SEE TEXT

DISCUSSION

1. In the last few years there has been a great impetus to the extension of artificial-pneumothorax treatment, together with other forms of collapse therapy in the care of pulmonary tuberculosis, so that the proportion of patients now receiving this form of collapse therapy is many times what it was a decade or more ago.

2. This very fact seems to render a dispassionate analysis of results, under various conditions and in various types of cases, all the more desirable, since many patients now receive this form of therapy who would not even have been considered ten or fifteen years ago. At the same time, however, some limitations are put on the accurate appraisal of end-results by the very reason of the relatively short period which has elapsed in many of the cases included in our study.

We find it difficult to locate or cite many comparable studies of similar nature, although the literature is immense. Among some of the most complete series we may refer to Brauer and Spengler (1911), Sachs (1915), Minor (1917), Kendall and Alexander (1918), Parfitt and Crombie (1919), Saugman (1913, 1921), Saxdorph (1921), Burrell and Macnalty (1922), Matson, Matson and Bisaillon (1923), Maendl (1924), Burnand (1924), Naveau (1925), Rist and Hirschberg (1926), Léon-Kindberg (1927), Peters (1928), Dumarest and Brette (1929), and Rist (1930).[2] Of these studies only those of Sachs and Maendl represented really composite groups from different sources. Although Sachs included

[2] We would also call attention to an important paper by LeRoy S. Peters: *Compression Therapy of Pulmonary Tuberculosis, Comparative Study*, AMERICAN REVIEW OF TUBERCULOSIS, January, 1929, xix, 74.

1,145 cases reported by 24 observers, the data were very incomplete and inadequate. Burrell and Macnalty's *Report on Artificial Pneumothorax*, published in 1922 and sponsored by the British Medical Research Council, while composite in the sense of quoting from many sources, does not attempt any uniform method of tabulation of the data sought by questionnaire. Forlanini, one of the first to collect extensive material, persistently refused to tabulate it. Saugman, in 1921, was able to report statistical results in a series of 310 cases; the Matsons and Bisaillon, in 1923, results in 600 cases over a period of twelve years. The number included by Rist and Naveau treated at the *Hôpital Laennec* in Paris approaches 750, also over a period of twelve years. Ringer, in 1922, and Rist, in 1930, discussed the matter of termination of treatment. Both Andrew Peters, in 1928, and, shortly afterward, Amberson and Riggins, in 1929, devoted some special attention to the late results of terminated cases treated at the Loomis Sanatorium. Here again we have but a single institution, although the records covered fourteen or more years. Maendl's study included about 1,400 cases, 230 of his own and 1,094 from responses to a questionnaire by 29 physicians in Germany, Austria and Czechoslovakia. He reviewed statistically 1,330 who had discontinued treatment, their pneumothorax dating 2 to 12 years back. Dumarest and Brette, in 1929, included in their book a chapter on the remote results of artificial pneumothorax, with reports on 229 out of 265 cases followed a considerable number of years. Armand-Delille and Vibert, also Knüsli, have reported on a limited number of cases in children.

The detailed findings of our study are presented in tables 1 to 18.

RESULTS AT TERMINATION OF PNEUMOTHORAX IN CASES WITH INTENTIONAL OR UNINTENTIONAL REËXPANSION

TABLE 1

Results at termination according to termination intentional or unintentional

	SYMPTOM-FREE		NOT SYMPTOM-FREE		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Termination intentional	69	59.4	47	40.6	116	36.6
Termination unintentional	72	35.8	129	64.2	201	63.4
Total	141	44.5	176	55.5	317	100.0

TABLE 2

Sputum at termination according to termination intentional or unintentional

	POSITIVE SPUTUM		NEGATIVE OR NO SPUTUM		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Termination intentional	39	33.9	76	66.1	115	31.9
Termination unintentional	130	53.1	115	46.9	245	68.1
Total	169	46.9	191	53.1	360	100.0

TABLE 3

Results at termination according to condition of treated lung before pneumothorax

	SYMPTOM-FREE		NOT SYMPTOM-FREE		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Cavitation considerable	65	50.0	65	50.0	130	36.9
Cavitation moderate, slight or none, or pneumonic consolidation	110	49.6	112	50.4	222	63.1
Total	175	49.7	177	50.3	352	100.0

TABLE 4

Sputum at termination of pneumothorax according to condition of treated lung before collapse

	POSITIVE SPUTUM		NEGATIVE OR NO SPUTUM		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Cavitation considerable	73	46.2	85	53.8	158	39.0
Cavitation moderate	46	45.6	55	54.4	101	25.0
Cavitation slight or none	34	35.1	63	64.9	97	23.9
Pneumonic consolidation	21	42.8	28	57.2	49	12.1
Total	174	42.9	231	57.1	405*	100.0

* A few cases appear in more than one classification.

TABLE 5

Sputum at termination of pneumothorax according to time of termination

PNEUMOTHORAX DISCONTINUED WITHIN	SPUTUM POSITIVE		SPUTUM NEGATIVE OR NONE		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
First year	108	63.6	62	36.4	170	48.9
Second year	25	25.2	74	74.8	99	28.4
Third year	11	23.9	35	76.1	46	13.2
After third year	8	24.2	25	75.8	33	9.5
Total	152	43.7	196	56.3	348	100.0

TABLE 6

Sputum at termination of pneumothorax according to condition of contralateral lung before pneumothorax

	SPUTUM POSITIVE		SPUTUM NEGATIVE OR NONE		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
No infiltration	34	28.6	85	71.4	119	33.1
Little infiltration	66	50.0	66	50.0	132	36.8
Moderate infiltration	61	59.2	42	40.8	103	28.7
Infiltration with slight cavitation	4	80.0	1	20.0	5	1.4
Total	165	45.9	194	54.1	359	100.0

LATER RESULTS

TABLE 7

Condition of pneumothorax patients one or more years after termination of collapse

INTERVAL AFTER TREATMENT	LIVING	DEAD	TOTAL	FATALITY RATE
1–2 years	347	49	396	12.4
2–3 years	328	19	347	5.5
3 years and over	303	25	328	7.6
Interval unknown	288	15	303	4.9
Total at end of period	288	108	396	30.4

TABLE 8

Condition of living patients one or more years after termination of pneumothorax according to (1) condition of contralateral lung before pneumothorax and (2) effective and ineffective collapse

	SYMPTOM-FREE ONE OR MORE YEARS				NOT SYMPTOM-FREE				TOTAL			
	Effective	Ineffective	Total	Per cent	Effective	Ineffective	Total	Per cent	Effective	Ineffective	Total	Per cent
No infiltration	58	14	72	83.7	4	10	14	16.3	62	24	86	43.6
Little infiltration	26	15	41	67.2	4	16	20	32.8	30	31	61	31.0
Moderate infiltration	16	13	29	60.4	4	15	19	39.6	20	28	48	24.4
Infiltration with slight cavitation	1		1			1	1		1	1	2	1.0
Total	101	42	143	72.6	12	42	54	27.4	113	84	197	100.0

TABLE 9

Ability of living patients to work one or more years after termination of pneumothorax according to (1) condition of contralateral lung before pneumothorax and (2) effective and ineffective collapse

ABILITY TO WORK ONE OR MORE YEARS AFTER TREATMENT	NO INFILTRATION		LITTLE INFILTRATION		MODERATE INFILTRATION		INFILTRATION WITH SLIGHT CAVITY		TOTAL			
	Effective number	Ineffective number	Effective number	Ineffective number	Effective number	Ineffective number	Effective number	Ineffective number	Effective		Ineffective	
									Number	Per cent	Number	Per cent
Able to work part-time	19	7	4	5	2	8			25	21.7	20	21.7
Able to work full-time	41	8	22	14	13	9	1		77	67.0	31	33.7
Unable to work	4	10	5	14	4	16		1	13	11.3	41	44.6
Total	64	25	31	33	19	33	1	1	115	100.0	92	100.0
Per cent able to work full- or part-time	84.3		70.4		61.5				74.0			

TABLE 10

Condition of living patients one or more years after termination of pneumothorax according to sputum at termination of pneumothorax

SPUTUM AT TERMINATION OF TREATMENT	SYMPTOM-FREE		NOT SYMPTOM-FREE		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Sputum positive	22	42.3	30	57.7	52	28.0
Sputum negative or none	115	85.8	19	14.2	134	72.0
Total	137	73.6	49	26.4	186	100.0

TABLE 11

Condition of living patients one or more years after termination of pneumothorax according to alterations in physical signs

PHYSICAL SIGNS OF TERMINATION OF TREATMENT	SYMPTOM-FREE		NOT SYMPTOM-FREE		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Râles diminished or disappeared	94	79.7	24	20.3	118	75.2
Râles increased	10	45.4	12	54.6	22	14.0
Râles unchanged	9	52.9	8	47.1	17	10.8
Total	113	71.9	44	28.1	157	100.0

TABLE 12

Mortality in relation to (1) duration of collapse and according to (2) effectiveness of collapse

PNEUMOTHORAX DISCONTINUED	DEAD		LIVING		TOTAL NUMBER	TYPE OF COLLAPSE				TOTAL NUMBER
						Effective		Ineffective		
	Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent	
Within first year	61	33.9	119	66.1	180	35	23.8	145	63.3	180
Within second year	20	18.0	91	82.0	111	58	39.5	53	23.2	111
Within third year	12	25.5	35	74.5	47	30	20.4	17	7.4	47
After third year	7	18.4	31	81.6	38	24	16.3	14	6.1	38
Total	100	26.6	276	73.4	376	147	39.1	229	60.9	376

TABLE 13

Mortality according to condition of contralateral lung before pneumothorax

	DEAD		LIVING		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
No infiltration	19	14.3	114	85.7	133	34.2
Little infiltration	49	34.0	95	66.0	144	37.0
Moderate infiltration	36	34.8	71	65.2	107	28.8
Infiltration with slight cavitation	3		2		5	
Total	107	27.5	282	72.5	389	100.0

TABLE 14

Mortality according to sputum at termination of pneumothorax

	DEAD		LIVING		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Sputum positive	77	47.5	85	52.5	162	44.8
Sputum negative or none	22	11.0	178	89.0	200	55.2
Total	99	27.3	263	72.7	362	100.0

TABLE 15

Fatality among patients with effective and ineffective collapse

	DEAD		LIVING		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Effective collapse	9	6.0	142	94.0	151	38.1
Ineffective collapse	99	40.4	146	59.6	245	61.9
Total	108	27.3	288	72.7	396	100.0

TABLE 16

Effectiveness of collapse in relation to age

AGE	EFFECTIVE COLLAPSE		INEFFECTIVE COLLAPSE		TOTAL NUMBER
	Number	Per cent	Number	Per cent	
Under 20	27	36.0	48	64.0	75
20–34	114	40.2	170	59.8	284
35 and over	10	25.6	29	74.4	39
Total	151	38.0	247	62.0	398

TABLE 17

Clinical condition at termination of pneumothorax according to age

AGE	SYMPTOM-FREE		NOT SYMPTOM-FREE		CONDITION NOT STATED		TOTAL NUMBER
	Number	Per cent	Number	Per cent	Number	Per cent	
Under 20	24	32.0	34	45.4	17	22.6	75
20–34	115	40.5	122	43.0	47	16.5	284
35 and over	6	15.4	20	51.3	13	33.3	39
Total	145	36.4	176	44.3	77	19.3	398

TABLE 18

Mortality in relation to age

AGE	LIVING		DEAD		TOTAL NUMBER
	Number	Per cent	Number	Per cent	
Under 20	58	77.4	17	22.6	75
20–34	201	71.4	81	28.6	282
35 and over	29	74.3	10	25.7	39
Total	288	72.8	108	27.2	396

CONCLUSIONS

1. Among the sanatoria which responded to our questionnaire the proportion of patients in whom therapeutic pneumothorax was induced or attempted varied from less than one per cent to thirty-four per cent, with an average of approximately ten per cent.

2. In our series exactly twice as many females as males received pneumothorax treatment. By far the largest number of these patients were between the ages of 20 and 35,—a distribution corresponding to the age-period of greatest frequency of pulmonary tuberculosis.

3. Approximately 40 per cent of the cases showed considerable cavitation, that is, destruction involving the collapsed or "treated" lung, and 25 per cent moderate cavitation, making a total of about two-thirds having more or less marked pulmonary destruction prior to beginning pneumothorax therapy.

4. The contralateral lung appears to have been essentially uninvolved in about one-third of the cases studied; slight lesions were recorded in a little over one-third; and moderate ones in a smaller group. Very few cases with contralateral cavitation were recorded.

5. In only a minority of the cases included (38 per cent) could an entirely effective collapse be obtained or maintained at all. (*Cf.* table 8.) This agrees, however, with the results of practically all the larger series previously reported by reliable observers.

6. The limitations on effectiveness above referred to are increased by the fact that in nearly two-thirds of the series studied it was necessary to discontinue treatment prematurely, most frequently because of the development of pleural complications, especially obliterative adhesions.

7. These two factors—(1) small proportion of cases susceptible to effective pulmonary collapse and (2) forced and premature discontinuance of collapse, usually by pleural adhesions—appear to limit most seriously the success of pneumothorax therapy and should be constantly kept in mind. There is always the tendency, especially in phthisis, to magnify successes, and to forget the indifferent results and the failures; and it scarcely seems warranted to promise more than is likely to be accomplished. On the other hand, the mechanical limitations to successful pneumothorax therapy should lead to an earlier consideration of supplementary surgical measures in those cases to which they are applicable.

8. Effectiveness of collapse of the diseased areas is the greatest single

factor in obtaining successful results, whether immediate or more remote. It seems obvious that valuable time is often lost in continuing over a long period a poor pneumothorax when other and more promising measures are available, or when the patient is obviously deriving no benefit from the procedure.

9. Other factors exerting important influence on the success of pneumothorax therapy are (1) duration of maintenance of effective collapse, (2) degree of involvement of the contralateral lung, and (3) disappearance and continued absence of tubercle bacilli from the sputum. This factor is, of course, more or less concomitant with the effectiveness of the collapse, though it may also be affected by developments in the contralateral lung. The advantage in the late results of the essentially unilateral group is clearly apparent in table 13.

10. It follows from the foregoing considerations that, as we continue to extend the indications for pneumothorax therapy, as has rapidly been done in recent years, we must expect a much larger proportion of unsatisfactory results, and may, in a certain group of cases, arrive at a point where it is questionable if there are any worth-while results. On the other hand, the point may always be raised that in the "desperate last resort" type of case an unpredictable few may derive unexpected benefit. However, it is at least urged that in all questionable cases further extension of indications be pursued with caution and not merely for the sake of trying something. The disadvantages of an unprofitable and fruitless pneumothorax should always be borne in mind.

11. Age of the patient does not, as far as these data show, exert an important influence on the success or failure of pneumothorax therapy. Although the number of cases in the lowest age-group is few, they furnish no substantial support for the common impression that patients under twenty respond poorly. In fact, the deviation in immediate results and in effectiveness of collapse favors those under thirty-five over the oldest group. These rather limited data suggest a wider use of therapeutic pneumothorax in the group under twenty, following the indications commonly employed in older patients.

12. The later results, in general, assessed one to fifteen years after termination of pneumothorax treatment, appear distinctly gratifying. Although a considerable number of patients could not be traced, over 70 per cent of those followed were still living and of these three-quarters were able to work. Thus, with due consideration of its very considerable limitations, artificial pneumothorax appears to be undeniably one of our

most valuable therapeutic measures in the treatment of pulmonary tuberculosis. We may further add that from this study its discontinuance seems warranted in many cases after a reasonably adequate period of effective treatment, which cannot be too dogmatically predicted.

In concluding, we desire once more to express our sense of appreciation to those institutions and physicians who have so generously contributed their data and records to make possible this study. The Committee also gratefully acknowledges the financial assistance of the American Sanatorium Association in the publication of the statistical tables of this report.

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BOOKS[1]

FRANCIS MARION POTTENGER: *Tuberculosis in the child and the adult. With 85 illustrations in the text, pp. iii + 611, St. Louis, The C. V. Mosby Company, 1934, cloth, $8.50.*

By MAX PINNER

During many active years Dr. Pottenger has been a leader in teaching the clinical features of tuberculosis by an impressive series of published papers, by numerous addresses, and by his well-known book, *Clinical Tuberculosis*. The present volume might well be interpreted as a desire to epitomize his experience and to hand it on to "an enlightened profession," as the dedication says. It is, according to the title-page, a discussion of pathological anatomy, pathological physiology, immunology, diagnosis and treatment. It is stated that a proper approach to the problem of the disease presupposes a basic concept of its nature. Although there is no reason to doubt that Dr. Pottenger has such a basic concept in mind, it is not clearly conveyed in this book; probably chiefly for two reasons. Many fundamental terms are used vaguely and equivocally; this is particularly true of terms relating to pathology and immunology. The exact meaning which Dr. Pottenger assigns to allergy, immunity, hypersensitiveness, and particularly to their problematical interrelationship cannot be

[1] THE REVIEW plans to carry a section devoted to *Book Reviews* from time to time. It accordingly invites contributions of this nature from any authors who may see fit to submit manuscripts and will be glad to accept those reviews that measure up to standards that would comprehend such features as thorough familiarity with the text of the work under review, as well as knowledge of the subject and field covered by the book; apposite comparisons with related texts; critical ability and treatment; good literary form; and helpful description of contents. Uncritical praise and repetition of publisher's "blurbs" will be as undesirable as savage or personal attacks; neither will be tolerated. The main—almost the sole—purpose of an acceptable review should be to inform and to entertain. No limits or restrictions will be set on length of manuscript or manner of treatment provided the above-mentioned general considerations are adhered to. All reviews must be submitted gratuitously and those accepted will be published without compensation. Manuscript should be prepared in standard form (typewritten, one side of sheet only, double-spaced, etc.), and according to the style set in the reviews printed above.

Any opinions expressed are to be considered as those of the reviewer alone, and the widest latitude consistent with probity, ordinary courtesy and fairness will be allowed in this respect. In no way are they to be regarded as representing opinions of the publisher or editors.

In general, reviews will appear under the reviewer's name, initials or pseudonym. If, however, good and sufficient reasons can be adduced, worthy anonymous or unsigned reviews may be published, provided the author's name is known to the editor.—*Editor.*

unravelled. There is no attempt at clear definitions. It is true, of course, that Dr. Pottenger is to blame not for creating this confusion, but only for perpetuating "a custom more honour'd in the breach than the observance." A fairly chaotic state exists, too, in the use of such words as bacillary dissociation, productive and exudative processes, and in the whole matter of cellular responses to the invasion of bacilli. If these basic topics are included in an essentially clinical book in a sincere attempt to provide a solid basis for clinical concepts, and not only as a perfunctory gesture to traditional completeness, the soundness of the entire book is gravely endangered when the chapters on pathology and immunology are marred by the inevitable consequences of loose and inaccurate terminology.

The second reason for the lack of lucidity is the fact that Dr. Pottenger evades issues by quoting diverging statements on a given subject without divulging his own opinion and without analyzing the merits of the contention. This is done to such an extent in the first few chapters, and again in the chapter which is unfortunately called "compression therapy," that the reader gains the illusion of reading an anonymous book.

But, there is no anonymity in the strictly clinical chapters. Here, Dr. Pottenger speaks with the authority based on his rich experience and careful bedside observation. His emphasis on symptomatology and on truly clinical methods is a welcome reaction against laboratory fadism. His chapters on visceral neurology of pulmonary tuberculosis will well repay careful reading, especially since Dr. Pottenger has not only originated this particular type of observation, but has, more than anybody else, elaborated this subject, and he shows lucidly its practical diagnostic applications. The discussion of light-touch palpation must be of great interest to every clinician, although Dr. Pottenger's results with this method may, for many, remain an aim impossible to achieve.

The important rôle of roentgenology in diagnosis is asserted, but its actual discussion is too brief, too conventional and not specific enough.

The therapeutic discussions, too, reflect the wisdom of long experience: much valuable information is given on general management and on treatment of symptoms. It is disappointing that the author did not see fit to discuss more specifically the results of tuberculin therapy in which he has probably more experience than anybody else in this country. Dr. Pottenger is an enthusiast for conservative therapy; his advice might be more convincing if he would publish some actual data on results of his therapeutic methods.

The chapter on collapse therapy seems rather out of date, not so much on account of its conservatism, occasionally interrupted by a grudging enthusiasm, but because it is inadequately brief, because it withholds from the reader much fundamental knowledge that *is* available, and finally because, in the complete absence of data on the efficiency of the various methods, the good and the ill

effects of surgical procedures are represented to be much more problematical than they really are.

The bibliographical references are adequate in mentioning the more important contributions; but it is regrettable that the foreign quotations contain numerous mistakes. On page 88, for example, a total of 11 foreign quotations contain 22 obvious errors and omissions.

For reasons mentioned, this book cannot be recommended to the student nor to the practitioner who wishes to make his first intimate acquaintance with tuberculosis; but the tuberculosis specialist, who will approach it with criticism, will find in it much valuable information.

VALDÉS LAMBEA: *Terapeutica fundamental de la tuberculosis. (Lecciones para médicos generales y estudiantes.) Pp. 223, Madrid, Imprenta, Juan Bravo, 3, 1934, paper, 10 pesetas.*

By ESMOND R. LONG

This volume is an amplified course of lectures on the various procedures followed in the treatment of tuberculosis, and impresses the reader as both a comprehensive and successful exposition of the field.

Unlike most texts on tuberculosis, it is limited to the field of therapy, leaving for other sources the subjects of pathogenesis, diagnosis and prevention. The opening chapter furnishes an historical background and orientation for the pages to follow. Especially interesting is the concise summary of the succession of remedies, which has brought us finally to the rest treatment and what the author considers a triumph of the times, gold therapy.

While in rest and hygiene the most rational treatment of tuberculosis has developed, Lambea stresses the grave abuses of the system, leading not infrequently to the neurotic patient for whom the cure becomes a life occupation. Inseparably bound with the question of rest is that of climate, and the mistakes in this respect are severely criticized. And, if one may suspect an outcrop of the traditional Spanish temperament in the preferential consideration of heliotherapy in comparison with more rigorous forms of outdoor treatment, few will disagree today with the outspoken censure of the "curas brutales al aire libre" or fail to approve the conservatism of the discussion of the "baño de sol" and the author's insistence on a proper understanding of case and technique.

The third of the six chapters reveals an understanding of biochemistry unusual in physicians devoting their major effort to tuberculosis. With a truly noteworthy assemblage of literature on the underlying principles in this field the author makes appropriate deductions for the treatment of tuberculosis. However, so great is the detail, even though correct, and so remote is much of it from direct application to tuberculosis, that the material in this chapter

seems disproportionate to the total content of the book. Practitioners will welcome, however, the specific sensible instructions for an adequate diet. The limitations of the Gerson-Hermansdorffer diet are made clear. The author's special knowledge of chemistry is again apparent in his description of calcium metabolism. His criticism of current extravagance in this field strikes the reviewer as thoroughly sound.

Considerable attention is devoted to tuberculin therapy, which Lambea finds one of the best specific measures in stimulative therapy. The chapter that is most interesting, perhaps because most open to question by clinicians in this country, is that devoted to chemotherapy. Whatever doubts the reader entertains on this subject, he will value the careful discussion of the underlying principles of the gold treatment. In denying the gold drugs bactericidal power *in vivo*, and attributing their action chiefly to a stimulative effect on the reticulo-endothelial system, the author adheres to the modern school. He admits the failure of the treatment in experimental animals, but considers its efficacy in man as proved. His instructions on preparations and dosage will be useful to all proposing to employ the treatment.

In the final chapter the various surgical procedures are discussed. This subject can hardly be presented adequately without illustrations, which are omitted from this volume, but the statement of principles is sound, and serves to round out the total presentation of the elements of treatment.

Altogether the volume furnishes just what its author intended, a simple expression of the fundamentals in the therapy of tuberculosis, with detailed consideration of certain fields.

RICHARD H. MILLER: *Tuberculosis of the lymphatic system. Illustrated, pp. xvi + 248, The Macmillan Company, New York, 1934, cloth, $4.00.*

By MAX PINNER

The title of this book suggests at once a number of fundamental and interesting problems in the biology of tuberculosis. There is, first of all, the strikingly different rôle that the lymphatic system plays in primary and secondary infections; there is the problem of retrograde lymphatic propagation; there is the question of lymphatic latency; there is the often-repeated suggestion of an antagonism between lymphatic and parenchymatous tuberculosis. But such principles are not discussed; and some are barely mentioned in this book in which "the author presents, in a practical way, the principal facts of interest in the biology and clinical features" of tuberculosis of the lymphatic system. In studying the book it is evident that the emphasis is meant to be on "practical," and that "biology" might as well have been omitted.

Dr. Miller's book has many grave shortcomings. It is often vague. It contains a good many statements that seem extremely doubtful, for which no

attempt at proof is made. It brings disappointingly little factual data from the author's rich clinical experience. Its style is so strangely awkward that the text is hard to read, and often hard to understand. There are many unnecessary repetitions. Some of the discussions pertinent to the subject are so superficial as to give no information.

These criticisms are so important that the reviewer feels the necessity of documenting them by examples from the book; these must needs be few, but they are chosen as representative examples.

Vagueness: "The red-cell sedimentation test is not specific, but it is thought that in well-marked cases the sedimentation rate (R.S.) is increased." Or, in the chapter on heliotherapy: "The patient is instructed to lie for a while, exposing the whole back; then to turn over, exposing the front of the body." Every phthisiologist has seen acute exacerbations directly traceable to such instructions.

Doubtful statements without attempt at proof: "The more general early removal of tonsils and adenoids" is one of "the reasons for the lessened incidence of glandular disease;" or

"The majority of cases of tuberculous nodes, as of other forms of non-pulmonary tuberculosis are caused by the bovine type of the bacillus." This statement is frequently reiterated, but no evidence is presented to support its correctness for this country and for the present time. Closely associated with this opinion is the statement that "in almost all cases of tuberculosis of the cervical nodes the infection has gained entrance through the tonsil or adenoid." A corollary is the advice that in all cases of tuberculous cervical adenitis (with few contraindications) "*Tonsils and Adenoids* should be removed." Since this has apparently been the routine in Dr. Miller's service he has had the opportunity to collect a valuable material on the incidence of tuberculous lesions in tonsils and adenoids and on the relative frequency of human and bovine infection. No mention is made of such studies. Had they been done they would probably have shown that following the pasteurization of milk the percentage of bovine infection in lymphadenitis is low. According to studies in New York City it was 12 per cent, and half of these 12 per cent were derived from out-of-town patients fed on raw milk.

Lack of factual data: Almost the only definite reference to the author's own experience is contained in eight brief tables on incidence, localization, complicating pulmonary conditions, and treatment.

Style: "Stokes mentions ten cases in which the primary lesions were either anatomical tubercle (post-mortem wart) or verrucosa cutis, and the lymph node infection being secondary, such cases are not like those with the skin lesions secondary to lymphatic disease."

Superficiality of discussion, a point that cannot be proved by quoting separated phrases, is evident particularly in the discussions on pathology, on heliotherapy and on tuberculin treatment.

Dr. Miller makes a strong plea for the more extensive use of radical surgery. Comparing his numerical results following conservative treatment and radical surgery, one finds but little difference. Among 89 cases, treated by radical excision, no lethal termination is reported. But of 116 patients who had been hospitalized, and they comprise, according to Dr. Miller's explicit statement, the surgically treated patients, 29 deaths occurred. It is, therefore, impossible to evaluate the results.

There is a total of 439 literature references, but many of them are not referred to in the text, and a considerable number of them have no apparent relation to the subject. On the other hand, certain pieces of work of signal importance are not mentioned at all.

The conclusion: Who shall read this book? Because of its sins of unreliable information and equivocation it should be on the *index expurgatorius* as far as students are concerned. The practising physician who has only the knowledge that he can derive from this treatise should be careful not to attempt the diagnosis and treatment of tuberculous adenitis.

FRIEDRICH WOLTER: *Das Tuberkulose-Rätsel von Pesterzsébet und seine Lösung vom epidemiologischen Standpunkt. With one illustration in the text, pp. i + 31, Leipzig, Georg Thieme, 1934, paper, M. 2.*

By MAX PINNER

Pesterzsébet is a suburban industrial slum town near Budapest in Hungary. In 1920 it had about 40,000, and in 1931 nearly 73,000 inhabitants. Dr Szalai started in 1925 to use Friedmann's vaccination in this community in a most extensive manner. In the years since, the tuberculosis mortality of Pesterzsébet showed a spectacular decrease. These are the simple facts that make up what is known in the European literature as the "tuberculosis riddle of Pesterzsébet." If the lively controversy were simply concerned with the question of whether the Friedmann vaccination was the cause of the drop in the tuberculosis mortality we should not be led to mention this matter here. Regardless of possible coincidental appearances, the Friedmann affair can be considered to be buried safely. But, as Dr. Wolter points out, the "tuberculosis riddle of Pesterzsébet" is none the less real for the possible intervention of a totally discredited method of treatment. In spite of extensive statistical correction it remains true that the decline in the tuberculosis mortality was astounding, particularly in a town in which poverty, lack of hygienic and hospital facilities, density of population and rapidly increasing industrialization constituted a constellation which should provide a hot-bed for tuberculosis. Obviously, such a community has the significance of an epidemiological experiment in which the various epidemiological factors can be studied and analyzed.

This is the task that Dr. Wolter undertakes in his present study. He shows —at least for this community—that the traditionally accepted variants that allegedly determine the incidence of tuberculosis must be relatively unimportant. Dr. Wolter, elaborating the ideology of Max Pettenkofer, emphasizes the significance of telluric influences (sanitation of soil, condition and depth of ground-water, etc.), and the importance of major climatic cycles. The fundamental discussion of such principles is to be found in previous publications by the same author; here he presents only a practical and specific application. These epidemiological principles are undoubtedly open to doubt and criticism; they have, as yet, found few followers. But that the traditional epidemiological approach to the problem of the major fluctuation in disease incidence may be inadequate, and may have to be changed or complemented; this seems rather convincingly demonstrated, at least with the example of Pesterzsébet.

JESSAMINE S. WHITNEY: *Death rates by occupation. Based on data of the U. S. Census Bureau, 1930. Edited by Jessamine S. Whitney, with 1 chart and 8 tables, pp. 32, New York, National Tuberculosis Association, June, 1934, paper, $1.00.*

By J. BURNS AMBERSON, JR.

Although limited statistical reports of this type have been published previously by life-insurance companies, this is the first time in the United States that death-rates by occupation based on federal census figures have been made available. The short text convinces one of the complexity and magnitude of the task which necessitated limiting the study "to death rates for occupied males, aged 15 to 64, for the year 1930 in ten states covering 53 occupation groups." Separate rates are given for 17 specific causes of death. The detailed tabulations were made by the United States Census Bureau. The hope is expressed that the result, here presented, may stimulate the planning of a similar but wider and more detailed investigation as a part of the next federal census. If so, the obvious scientific spirit in which the present study was conceived and executed may well serve as an example to be emulated.

Death-rates are standardized for age, thus increasing the value of the figures which are assembled in eight tables. These are easy for study and will surely arouse a curiosity for their implied meaning among students of disease, public health and social welfare.

A striking finding is this: "Although . . . . tuberculosis is now seventh in rank in the country as a whole as a cause of death, this table (6) shows that it is the second cause of death among men aged 15 to 64 in the United States, and also the second cause of death among gainfully occupied men in the same group." Since the ten states considered comprise 38 per cent of the whole population it seems safe to draw this wide inference.

A point of interest is that the tuberculosis death-rate, in the 24–44 age-group, for instance, fluctuates widely from a low of 20.3 per 100,000 among lawyers, judges and justices to a tenfold high of 238.6 among factory and building-construction laborers. Closely paralleling, as they do, the descending economic scale these rising rates are eloquent for the strong influence of environmental factors on tuberculosis incidence. Such findings, properly interpreted and applied, will surely give more direction and force to the anti-tuberculosis campaign.

Among all occupations listed in table 8, one of the lowest death-rates from tuberculosis is among physicians and surgeons. They are bettered only by such classes as lawyers, bankers and brokers, and their standardized rate of 23.7 per 100,000 compares with 87.5 for all groups as a whole. Since the hazard of developing tuberculosis is considered, by some, to be great for those who care for the tuberculous sick, one wonders why this is not reflected in these statistics. In this respect the figures suggest that, after passing puberty, one's place in the social-economic order is of vastly greater importance than his personal contacts. The argument that low social-economic status is synonymous with more contaminated contacts and other evidence to the contrary should be more thoroughly weighed against this study and others which it is hoped will follow before spreading great alarm among those whose duty brings them into the presence of the afflicted.

These citations indicate the potential usefulness of the study. The National Tuberculosis Association is to be commended for sponsoring projects of such intrinsic worth.

RAUL A. PIAGGIO BLANCO AND FEDERICO GARCÍA CAPURRO: *Estudio etiólogico y topográfico de los procesos localizados del tórax. With eight full-page plates, pp. 52, Montevideo, Industrial Grafica, 1933.*

By ESMOND R. LONG

This monograph is an outgrowth of experimental and clinical studies made by a group of investigators in the surgical clinic of H. García Lagos, who supplies an introduction characterizing the work as a new type of topographical anatomy based on radiology. As a result of an ingenious technique the authors have localized the interlobar planes in relation to the bronchi to the various lobes. Experimental studies were carried out on isolated lungs and lungs exposed within the thorax of the cadaver. The bronchi were marked by injections of radio-opaque oil, and the interlobar fissures by the interposition of sheets of lead, and the relation of the two was determined by frontal and profile radiography.

Application of the results secured is illustrated by citation of several cases in which diagnoses of location, based on bronchography, were confirmed at operation or necropsy. The importance of profile bronchography is stressed.

The monograph can be well recommended for study as a modern contribution to anatomy, facilitating the localization of chest lesions and furthering surgical precision.

OTTO GLASSER: *Wilhelm Conrad Röntgen and the early history of the röntgen rays, with a chapter on personal reminiscences of W. C. Röntgen by Margret Boveri. Illustrated, pp. xii + 494, Springfield, Illinois, Charles C. Thomas, 1934, cloth, $6.00.*

By MAX PINNER

Since its first publication in German, Doctor Glasser's book has received so much justified acclaim that nothing could well be added to its recommendation. Its careful documentation and its pleasant style have been praised. It might, however, be emphasized that the real significance of this book is the fact that it is principally a biography of the invention and not the inventor. The choice between the two alternatives of putting the man or his work in the centre of the stage was made wisely, if not by sheer necessity. The invention of the roentgen-rays has fired imagination probably more than any other scientific invention; its repercussions were general and seemingly boundless; the scientific and human response to it was immediate and feverishly enthusiastic. In witness thereof Doctor Glasser has collected a list of 1,044 scientific publications on roentgen-rays that appeared in the year 1896 (which, incidentally, would indicate a greater editorial speed in 1896 than in 1934). Compared with the profound stir that the invention caused there is but little of interest in the inventor. Doctor Glasser has undoubtedly collected all the data available about Wilhelm Conrad Roentgen; Margret Boveri, a close friend of the Professor, has added a chapter of personal reminiscences and letters, and her account must contain as many intimate glimses as could be had from a man as reticent and uncommunicative as Roentgen was. The combined picture is sympathetic and demanding of respect; but still it leaves the reader peculiarly unsatisfied. The relation between the nature of the man and his stroke of genius, his invention, is not apparent. There is nothing in Roentgen's mental stature, as far as the book informs us, to expect the genius; nothing to make it understandable why he of all men was destined to be this great inventor. It is most likely not the fault of this biography that the psychological relation between inventor and invention remains obscure, and it is surely not an argument against Roentgen's greatness; but it is a striking demonstration of our profound ignorance of what may be called the anatomy of genius.

Roentgen refused consistently to allow his invention to shape materially, or to alter the calm sequence of his academic life; he gained no wealth from his work that made millions for many, and he accepted only the unavoidable honors that were showered upon him. But he insisted energentically on his priority and rejected with force the many apocryphal stories that tended to

belittle his share in the invention. Doctor Glasser has, probably successfully, refuted all those stories about laboratory *Dieners* and assistants. It is a curious fact which again emphasizes the apparently unvital relation between this man and his work, that Roentgen published only three or possibly four brief papers on his rays and that the last of these appeared fourteen years before his last scientific publication.

Roentgen, like many another great scientist, was a poor and uninspiring lecturer. Nothing expresses this fact more unequivocally than a Munich students' ditty, said to have been carved into a desk in Roentgen's lecture room at the University of Munich. It used to be so popular that it can hardly be unknown to Dr. Glasser who, as does the reviewer, withheld it from publication obviously in deference to propriety and out of respect for Roentgen.

As a story of an invention of limitless consequences, Doctor Glasser's book makes excellent reading. In spite of many minute details, interest never sags. The translation is well done. But at some time it should become known to all German-English translators that *Hochschule* does not mean high-school.

The publishers have done a beautiful job of typography, binding and illustrating.

OTTO GLASSER: *The science of radiology. A symposium by 25 authors. Edited by Otto Glasser. With 108 figures in the text, pp. xiii + 450, Springfield, Illinois, Charles C. Thomas, 1933, fabrikoid, $4.50.*

By AARON EDWIN MARGULIS

By the admission of the triumvirate responsible for its appearance, this book is an indirect outcome of the Chicago Century of Progress Fair. The announcement of that exposition gave impetus to an already germinating plan to fuse four national radiological organizations into an American Congress of Radiology. The Congress met and organized itself into ten committees, one of which (a commendable precedent) was a *Committee on History and Education* with Byron Hubbard Jackson as Chairman. The Executive Council of the Congress charged this committee with the preparation of a monograph which would outline the outstanding features of the development of the science of radiology from the eventful day in 1895, when Roentgen first placed a fluorescent screen before a Crooke's tube in a darkened room, to 1933. The objective was history and not a textbook.

It is not often that youngsters of 38 years pause to survey their rapidly developing selves, but decidedly radiology is medicine's most precocious ward. In this instance the stock-taking is not a self-examination for purposes of reevaluation and reorientation, nor a smug recounting in self-satisfaction with contemporary achievement. Herein is a straightforward tale of an epigenesis, and the completed story (to 1933) finds apparently even its votaries, as one of them admits in an introductory paragraph, amazed at the ramifications of the edifice in process of erection.

The committee was fortunate in obtaining the services of Otto Glasser, the biographer of Roentgen, as editor. Under his supervision twenty-six distinguished authors contributed twenty-five splendid chapters. Short biographical sketches of Roentgen and the Curies, the physical basis of the science, the development of apparatus, dosimetry, diagnosis, biological effects of radiation, pedagogical consideration, industrial application, and the history of radiological studies and literature, are some of the topics treated. Since the term "radiology" is here construed in the broadest sense, discussions of cosmic rays, Gurwitsch rays, visible, ultraviolet, and infrared radiation, are also included.

The chapters are uniformly good. However, some of the authors carried out the original intent, that is, an historical survey, better than others who devoted more space to and placed greater emphasis on factual features of present-day status of knowledge. Most give the reader the impression of having attacked their task with enthusiasm and to have put into it a great deal of bibliographic research and effort, all the chapters being adequately documented. In this connection the reviewer cannot refrain from singling out Percy Brown's chapter on *Radiological Diagnosis* for its internal evidences of meticulous scholarship and arduous labor. This chapter alone has a bibliography of over 500 items. One wishes, however, that J. Burns Amberson's pioneer work in popularizing serial roentgenography in the study of pulmonary tuberculosis had not been overlooked.

The success in keeping this volume within reasonable size, despite the ground covered, further attests to the wisdom of its editorial policy and the good judgment and coöperation of its contributors. The publisher too has done his part well and the book will be an attractive as well as a distinctly worthwhile addition to the library of the student who realizes that his grasp of the present is tempered by his knowledge of things past.

ROBERT W. BUCK: *The essentials of physical diagnosis. With twenty-one illustrations, pp. 259, Philadelphia & London, W. B. Saunders Company, 1934, cloth, $3.00.*

By BENSON BLOOM

This short volume on physical diagnosis attempts to present to students the various methods of examination, not only of the heart and lungs, to which most such works ascribe practically all of their attention, but to the head, abdomen and extremities as well. Other sections are devoted to such important, but frequently neglected, factors as posture, gait and the psychic state of the patient. The presentation of such adjuncts to diagnosis as the electrocardiogram and the roentgenogram is deliberately omitted, since such discussions are felt, by the author, to belong to the field of general medicine. Likewise, pathological descriptions are not included. The result is a well-written, simple,

concise book which students should appreciate. The clear explanation of eponyms is instructive and interesting. As is to be expected in such a short volume there are a number of instances in which a more complete discussion would be desirable. For example, after describing the causes of functional heart murmurs, the unsatisfactory statement is made that "they are usually systolic in tone." The practising physician may well prefer a more extensive work than this for reference, but it is completely adequate for the medical student who will certainly enjoy the practical way in which the volume is written, and the many helpful methods of examination it describes, some of which, as far as the reviewer is aware, are not described in the usual textbook, although commonly used by many physicians; for example, the methods described of palpating the spleen and the liver.

NEUTON S. STERN: *Clinical diagnosis, physical and differential. Pp. xviii + 364, The Macmillan Company, New York, 1933, cloth, $3.50.*

By ROLAND DAVISON

Dr. Stern has undertaken a difficult task in attempting to present in a book of 364 pages the essentials of clinical diagnosis. In the first part he gives the technique of history taking, the technique of making a physical examination with a brief recitation of the best method of procedure, and the pathological conditions the examiner may encounter. The second part of the book is devoted to the diagnosis of tuberculosis and heart disease; the third part informs the physician how to proceed in the study of a given patient to make a diagnosis; and the fourth part of the book is an alphabetical list of symptoms and signs with subheadings showing the significance of the particular symptom or sign, and the disease conditions in which it is encountered.

The outlines of the various methods which should be used in the study of a particular system which are given should be very helpful to beginners, but the actual procedures are inadequately described, and many physical signs are not described at all. Only ten pages are devoted to the symptoms and signs of tuberculosis.

Throughout the book one finds many omissions, with resulting disproportion and incompleteness.

HAROLD A. ABRAMSON: *Electrokinetic phenomena and their application to biology and medicine. With frontispiece, 56 tables and 105 figures in the text, pp. 331, American Chemical Society Monograph Series, Chemical Catalog Company, Inc., New York, 1934, cloth, $7.50.*

By AARON EDWIN MARGULIS

Of the many possible approaches to the problems of biology, that which employs the methods and the ideology developed in the study of inorganic prob-

lems is still enjoying the greatest vogue. Since it is fairly generally accepted in our present intellectual milieu that solutions are functions of the methods by which they are derived and are therefore characterized by arbitrariness, expediency, and that sufficiency which might be termed psychological satisfactoriness rather than by pretensions to descriptions of absolute reality (whatever that term may signify), it is necessary to scrutinize the operational derivation as well as the content of such approaches. The concepts employed by the physicists and chemists were derived by operations performed wholly outside of the biological domain. One may therefore view the investigation of biological phenomena with the tools of the investigator of the inorganic as destined to be essentially arid, as do biologists like J. S. Haldane, to whom biology must retain a peculiar autonomy for satisfaction in formulation. On the other hand, one might be curious and patient about the fruitfulness of such investigations, viewing them ultimately as a temporary expedient, without relinquishing for a moment the firm belief that a synthesis of biological and nonbiological ideology is desirable, possible, and preferable to either description of the former in the language of the latter, or autonomy for each. The desideratum is a single set of primitive assumptions from which satisfactory word pictures of both the living and the nonliving might be erected. With these thoughts in mind, the significance of Dr. Abramson's book may be more correctly evaluated.

To account for the special properties that surfaces present, physical chemists have postulated that the molecules bounding interfaces are oriented in a specific manner. One method of studying the structure of such interfaces is to measure the difference in potential existing between phases when tangential motion occurs between them. This method is termed *electrokinetics*. These ideas and methods are of major interest to biologists, for the microscope and the tools of the analytical biochemist have demonstrated liquid-solid, solid-solid, and other interfaces in living matter, and the phenomena occurring at these surfaces (permeability, absorption, excretion, etc.) are among the most fundamental and complex with which the biologist has to deal.

Dr. Abramson has reviewed and summarized the work done to date by electrokinetic methods on the chemistry and physics of surfaces with emphasis on biological applications. The quality and quantity of work extant, and the absence of any existing similar tract in the English language, amply warrant the undertaking. Although the book is cast in the conventional form, the treatment is far from perfunctory. One is almost immediately convinced that the author has thoroughly digested that of which he writes. History, theory, and methods are first presented, sufficiently rather than exhaustively. The historical introduction is particularly well done, and will be especially valuable to those to whom understanding is achieved by knowing the present as something evolved step by step rather than as something given. The work on the simpler inorganic and organic surfaces is next reviewed, and then the more complex ones of living cells, immune bodies, etc.

Dr. Abramson rightly, I think, does not try to "spare" the reader by avoiding mathematical formulations, although he will undoubtedly thereby incur the criticism that the book would have been more useful to biologists if it were more descriptive and less mathematical. If mathematics is introduced into a discipline, obviously it is done so for good and sufficient reasons. The reversal of this procedure in deference to those mentalities who are bored or awed by mathematics, is a misleading concession. Mathematics is the descriptive language *sine qua non* and Science as well as Literature loses in translation. Moreover Dr. Abramson nowhere interests himself in the mathematical *form* of ideas to the exclusion of interest in their content.

Further discussion of the contents of the book is not warranted here. As regards the general significance of this methodology in biological research, Dr. Abramson expresses the belief that these studies will eventually disclose mechanisms of many phenomena still held mystical by virtue of their occurrence at phase boundaries, and, more specifically, that they contain the possibility of simplifying immunological problems,—which is tantamount to admitting that decision must be reserved. Obviously, unless some such achievements come about, the method will fall into disuse. It is also obvious that the probability of "simplification" of problems is not only dependent upon detail work, hopefully expected to be done in the future, but also upon the question as to whether the primitive notions behind the terms in which the solutions would be cast would be acceptable as "explanations" to biologists. In short, would the simplification be more apparent than real? Although the answer to this question is susceptible of prognostication, in part at least, by suitable investigation, possible in the present, nowhere, unfortunately, do we find discussion of the point. Perhaps the book as a whole was meant to answer these questions. If so, the reviewer's tentative reaction would be "interesting," rather than "informative," in so far as biology is concerned. To convince oneself on this point, one need but pose a problem and contemplate an hypothetical answer, such as electrokinetics might yield. Perhaps as extenuation for failure to discuss these matters would be pleaded that as an American Chemical Monograph this book is intended for scientists not primarily interested in such quasimetaphysical problems. However, awareness is most certainly growing that such considerations may not with impunity be relegated to the professional philosophers, that is, without placing disastrous limitations on the ultimate value of pure science *per se*. The mathematicians learned this lesson a century ago, the physicists are currently courageously struggling with such problems already with brilliant results, while the biologists only in dishearteningly few instances seem aware of the problems' existence at all. At least the active discussion of these questions would be a sign of vitality, while the reverse, contentment for overly long periods with filagree work within outlines already laid down, is a symptom of intellectual decadence.

THE NATIONAL ORGANIZATION FOR PUBLIC HEALTH NURSING: *Survey of Public Health Nursing. Pp. i–xv, + 1–262, The Commonwealth Fund, New York, 1934, cloth, $2.00.*

By VIVIAN TAPPAN

In the present period of financial depression it seems particularly fitting that a survey of public-health nursing should have been made. For under existing conditions of economic pressure the problems of public health become aggravated, and the need of an efficient well-coördinated, clearly defined organization becomes correspondingly urgent.

An effective public-health organization depends on the integration of its separate parts, and during the more recent years the public-health nurse has played an increasingly important rôle in the coördination of public-health projects and civic activities. She has become a fairly familiar figure in school work, in the control of infectious diseases in the home, in prenatal care, and in postpartum follow-up work. Very few individuals appreciate to what degree she requires a highly specialized training for the all-embracing character of her work, and even fewer understand the methods and procedures by which she functions as an effective unit as measured in terms of social results.

A little like Topsy she has "growed up," and in the present complexity of social-welfare organizations, her position is frequently anomalous. Just how anomalous remained for this *Survey of Public Health Nursing* to demonstrate. Although a statistical study, its figures are well correlated in orderly intelligible columns, and in the text simple clear-cut statements point up essential facts. The conclusions are inevitable that the present training of the public-health nursing personnel is inadequate at least in part, and that the organization of the public-health nursing service of to-day falls short of the demands made upon it. The present growth of public-welfare work with its new necessities has outstripped the nurse of the old school. Her contributions, as well as those of the organization she represents, are recognized, and well-deserved credit is given to them. But, in order to meet the more recent developments, a far more rigid training in particular nursing is advocated, and a course in civic economics becomes essential. Finally the public-health nursing service must lose in some measure its present absolute identity, and become merged in the greater communal welfare organizations.

The findings of the *Survey* are destructive only in their frank admissions of the present inadequacies of the public-health nursing system. They are constructive in the specific recommendations with which they counter each criticism which they have previously offered.

The book makes interesting reading despite the categorical nature of its subject matter. It widens the scope of civic knowledge for the average lay individual, and it should serve as an invaluable guide not only to public-health workers, but to everyone engaged in civic welfare work.

THE STAFF OF THE MARY IMOGENE BASSETT HOSPITAL, COPPERSTOWN, N. Y.: *Clinical miscellany. Pp. 1–206, C. C. Thomas, Baltimore, Maryland, 1934, cloth, $3.00.*

By VIVIAN TAPPAN

Clinical Miscellany establishes a new and interesting form of medical publication. According to the preface the book represents an effort to activate fragments of experience in the portrayal of clinical material selected from case-records of the Mary Imogene Bassett Hospital. Clinical cases are presented very much as one might find them at the bedside, in clinical pathological conferences, or in the *Cabot's Case Records*. No new or startling facts are offered, and no extremely rare or exotic pattern of disease is depicted. The volume deals with the less usual rather than with the bizarre. Thus the clinical picture of meningococcaemia complicated by nephritis, of botulism, of undulant fever, of sulphaemoglobinaemia, are among the cases clearly outlined. The clinical notes are not infrequently illustrated by photographs, X-ray plates, or corresponding charts. Any experimental work undertaken in an attempted diagnosis of a case, or in the treatment of a patient is briefly given. Postmortem notes if available are added. A short discussion usually closes each case report.

These discussions are limited for the most part to a few practical salient points. One regrets that in all instances the field of comment was apparently so restricted by design. This is especially true in the instances of the case-reports by Dr. Mackenzie, where one feels the conscious limitation of interesting discussion and valuable opinion by a conscientious adherence to the principle not to extend the scope of comment beyond terse statements of existing facts or theories.

However, this criticism may be unwarranted, as the reader is warned that only a small increment of medical knowledge may accrue to him. The justification of the volume lies in the medical growth of those contributors who, through study, have attempted to correlate and record their own experience. The reader may correspondingly share in these benefits provided he in turn measures his personal medical experience against the clinical material, in contrast to or in confirmation of that presented to him in the book.

Clinical Miscellany is compiled by members of the staff of a small hospital somewhat isolated from a large city. In its inception and execution it is an expression of an active interest taken in the academic phase of the practice of medicine. As such alone it is worthy of emulation. In addition the book adds further proof of the protean manifestation of disease, and it constitutes a new source where one may turn for descriptive data bearing on the more unusual clinical entities.

Brief Comment

H. D'HOUR: *La radiologie des scissures pulmonaires. With a preface by Prof. L. Langeron, with 53 plates and 152 figures in the text, pp. 180, Paris, G. Doin & Cie., 1934, paper 75 fr.*

A monograph on the anatomy and roentgenology of the pulmonary fissures. The pathological processes which are located in or limited by these structures are discussed clinically and roentgenologically. This study is documented by a large number of excellent illustrations.

J. BURNS AMBERSON, JR., GODIAS J. DROLET, FOSTER MURRAY, HENRY C. WRIGHT, HAVEN EMERSON: *Report on the hospitalization of the tuberculous to S. S. Goldwater, Commissioner of Hospitals of the City of New York. Pp. 53, Committee on Hospitalization of the Tuberculous, New York, 1934.*

A report which is a model for clarity in thinking, the surety of its grasp of the problems faced, the straightforwardness of its recommendations, and the lucidity of its presentation. The important proposals are (1) centralized correlated control of all phases of community responsibility toward the tuberculous, (2) decentralization of facilities, and (3) a total bed-capacity equivalent to one and one-half beds per death from tuberculosis.

Books Received

DIETLEN, HANS: Die Lungentuberkulose. Medizinische Praxis, Band xvii, with one illustration, pp. xiii + 149, Dresden and Leipzig, Theodor Steinkopff, 1934, paper, price Mk. 8.

FERRARI, VIRGILIO: Il pneumotorace bilaterale. With an introduction by Prof. Maurizio Ascoli, with 15 plates, pp. 145, Milano, Sperling & Kupfer, S.A., 1933, paper, price L. 35.

NUZUM, FRANKLIN R.: The span of life. Pp. ix + 108, Springfield, Ill., Charles C. Thomas, 1933, cloth, price $2.00.

PABLO, VICENTE DE: Medicacion local pulmonar por via intratraqueal. With a foreword by S. Garcia Vicente, with 21 plates, pp. 56, Buenos Aires, Aniceto Lopez, 1933, paper.

PFAFF, WILHELM: Der Ausbau der Tuberkulosetherapie. With an introduction by Dr. Kurt Klare, pp. vii + 102, Stuttgart, Ferdinand Enke, 1933, paper, price Mk. 6.

SEWALL, HENRY: Society and the natural law. Pp. 79, Boston, Richard G. Badger, 1933, cloth.

WINSLOW, C.-E. A.: A city set on a hill. With foreword by Holmer Folks, pp. xvi + 367, Garden City, New York, Doubleday, Doran & Co., Inc. (published for The Milbank Memorial Fund), 1934, cloth, price $3.00.

ELLIS, ANNE: Sunshine preferred. Pp. 249, Boston, Houghton Mifflin Company, 1934, cloth, price $2.00.

THE ROENTGEN-RAY APPEARANCE OF THE LUNG FIELDS IN ATELECTATIC BRONCHIECTASIS[1]

RICHARD H. OVERHOLT

If the diagnosis of bronchiectasis can be approached more closely by a study of the plain X-ray film alone, the greater will be the frequency that the condition will be recognized. Although the value of the plain roentgenogram in the diagnosis of bronchiectasis has been minimized, there are certain features of the plain film which strongly suggest bronchiectasis, and therefore may be valuable in the segregation of such conditions. It is the purpose of this paper to emphasize the importance of the difference in the lung fields in the uninvolved portions of the lung in cases of bronchiectasis affecting the left lower lobe, and also to emphasize the value of ascertaining the position of the posterior leaf of the diaphragm, as shown in the lateral roentgenogram.

The most constant feature of the roentgen-ray picture is the presence of an increased density of the peribronchial markings. If the dilatations of the bronchi are saccular, thick-walled, or filled with secretion, they may be detected as circular shadows. If the bronchiectasis is of the cylindrical type, it is more difficult and often impossible to diagnose from a plain X-ray film. The roentgen-ray appearance of bronchiectasis has been described by Holmes and Ruggles (1) as being one in which there is "thickening of the lung markings along the course of the larger bronchi, and enlargement of the hilum shadow with the presence of single or multiple areas of increased density in the lung fields near the bronchi." Ballon, Singer and Graham (2) limit their description of the appearance of the plain roentgenogram to the following statement: "Increased hilus detail, which extends down to the base, and circular shadows are very suggestive of bronchiectasis, although the former may be only branches of pulmonary vessels."

The particular alteration in the appearance of the plain roentgenogram in unilateral bronchiectasis to which attention is directed in this paper is produced largely by the altered relationship in the size of the healthy and the pathological lobes of the lung. Partial or complete atelectasis,

[1] From the Department of Thoracic Surgery, Lahey Clinic, Boston, Massachusetts.

fibrosis and shrinkage of the involved lobe are a part of the pathological picture in bronchiectasis. Studies of bronchiectatic lobes, removed surgically or postmortem, have invariably revealed a pulmonary lobe diminished in size. A recent report upon such material has been made by Erb (3). The occurrence of a contracted pulmonary lobe in bronchiectasis has been recently discussed by Jones and Cournand (4) in an article entitled *The Shrunken Pulmonary Lobe with Chronic Bronchiectasis*. It has been the experience of the author and of others (5) (6), in doing pulmonary lobectomy for bronchiectasis, to find the diseased lobe indurated, soggy to palpation, and definitely reduced in size. The fibrosis may be so extensive that the lobe has become completely collapsed, and may occupy only a small area in the lower and medial portion of the hemithorax, with compensatory expansion of the upper lobe to fill the remainder of the chest.

A collapsed lower lobe is well recognized by roentgen-ray as a dense triangular shadow at the base of the chest, with the apex of the shadow at the hilum and the lateral border curving downward and outward to the diaphragm. This appearance in atelectatic bronchiectasis has been described by Singer and Graham (5), Rist, Jacob and Trocme (7), and Pinchin and Morlock (8). An excellent description of the triangular roentgen shadow in bronchiectasis has recently been given by Warner and Graham (9). Singer and Graham (5) and Kerley (10) also call attention to compensatory distention of the upper lobe. Reference has not been made, however, to the importance of the study of the relative density of the lung fields in the uninvolved portions of the chest on the two sides as an index to partial or complete atelectasis of a lower lobe. The cases reported here show that this is an especially valuable aid when the associated collapse is not sufficient to cast a dense shadow and in left-sided lesions when the shadow of an atelectatic lobe is obscured by the heart shadow. Sante (11) has pointed out that bronchiectatic involvement in such a situation may entirely escape detection in the ordinary film.

The value of a lateral roentgenogram in such cases lies principally in the fact that it indicates the position of the posterior leaf of the diaphragm. If there is a reduction in the size of one of the pulmonary lobes, an elevation of the posterior leaf of the diaphragm occurs as the first response of the walls of the hemithorax to accommodate for a smaller lung. Some elevation or distortion of the posterior leaf of the diaphragm is a constant finding when a pathological condition has caused

shrinking of one of the overlying pulmonary lobes. An alteration in the position of the diaphragm may not be apparent in the usual P-A (postero-anterior) view and may be overlooked on fluoroscopic examination. A true lateral roentgenogram of the chest with the patient in the erect position has been found to be a reliable way to demonstrate the actual relative position of the posterior leaves of the diaphragm.

Three cases illustrate the significance of these two points in the roentgenographic examination of cases of unilateral atelectatic bronchiectasis. In two tuberculosis had been suspected. Roentgenograms of the chest showed a perfectly clear lung field on the left without apparent abnormality of the hilum shadows. The right lung field showed a relative increase in the density of the lung markings and an apparent intensification of the bronchial markings and definitely a more dense hilum shadow on the right than on the left. From the X-ray appearance alone, the question of a diffuse hilar type of tuberculosis in the right lung had been raised.

Cases

1: A boy, aged twenty years, a patient in the New Hampshire State Sanatorium was referred by Dr. Robert Deming. He had been admitted five years previously on account of suspicion of tuberculosis because of chronic cough, expectoration and weakness. There was no history of haemoptysis. He had never been seriously ill, and had not had any serious infection of the upper respiratory tract previously. He had never had an attack of pneumonia. Through his entire stay in the sanatorium, he had been languid and became fatigued easily. He was quite satisfied to lead the invalid life of the sanatorium. There was practically no improvement in his condition and he continued to raise between three and four ounces of sputum each day. Physical examination revealed a thin, stoop-shouldered lad of twenty years with sallow complexion. He did not show cyanosis. There was moderate clubbing of the finger-tips. The examination of the head and neck was essentially negative. The expansion of the chest was somewhat limited but equal. The excursion of the diaphragm was slightly restricted on the left and normal on the right. There was some impairment of the percussion note over the left base posteriorly. Upon auscultation the entire right chest and upper left chest were negative. Coarse, sonorous and bubbling râles could be heard in the posterior inferior left chest. The remainder of the physical examination was essentially negative. The sputum examinations were repeatedly negative for tubercle bacilli. Roentgenograms of the chest, taken repeatedly over a period of five years, showed very little variation in the lung picture. The chest was symmetrical without deformities of the bony framework. The

boundaries of the right lung were normal in outline. It is important to note, however, that the lung markings, the peribronchial and hilum shadows on the right side, were considerably more dense than on the left. The entire left lung fields were clear, and, in contrast to the right, the shadows were

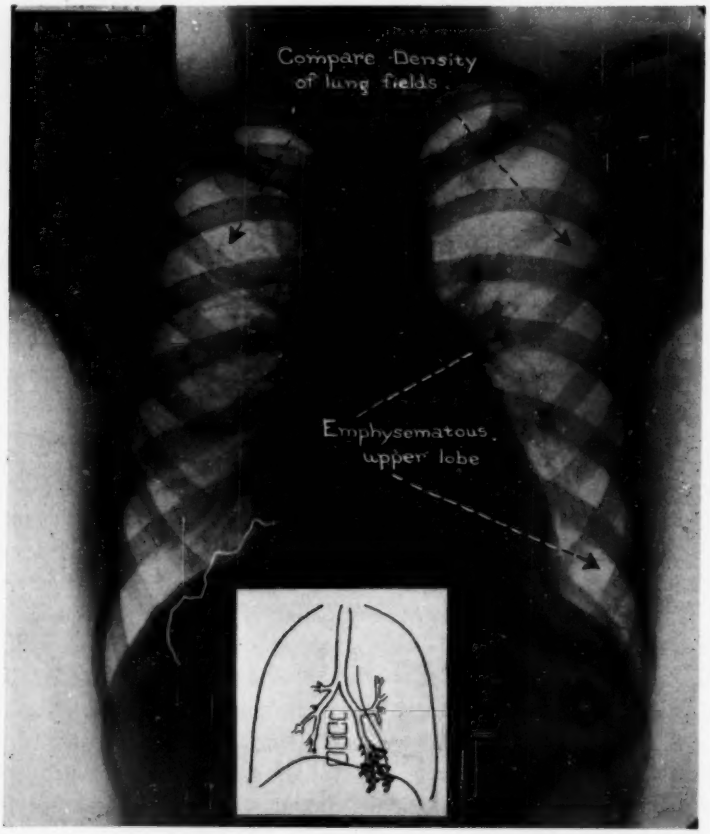

FIG. 1. Roentgenogram in case 1 showing left lower-lobe bronchiectasis. Insert shows reproduction of lipiodol bronchogram. Note the difference in density of the hilum shadow and lung fields on the right and left sides. The bronchiectatic lobe is entirely hidden by the cardiac shadow. The left upper lobe is hyperexpanded to fill the entire left hemithorax. The relative level of the diaphragmatic domes is normal.

diminished in density by approximately 50 per cent (figure 1). Injection of lipiodol, and X-rays following aspiration of the tracheobronchial tree by bronchoscopy, revealed many small bronchiectatic cavities, and a shrunken atelectatic left lower lobe. The ramifications of the left lower bronchi were limited

to the area behind the cardiac shadow. The secondary divisions of the left upper bronchus were distributed to its lobe, which occupied the entire portion of the left hemithorax, except for that small portion behind the cardiac shadow. A subsequent injection of the right tracheobronchial tree showed no abnormality. A diagnosis of unilateral left lower atelectatic bronchiectasis was made.

2: A woman of thirty-five years of age was referred by Dr. Garnet Smith of the Bristol County Hospital at Attleboro, Massachusetts. The patient's first pulmonary symptom dated back fourteen years, at which time an initial sudden haemoptysis was followed shortly by several minor haemorrhages. She had fever for many weeks. A pneumothorax was attempted unsuccessfully, on the left side. She was in a sanatorium for thirteen months. Three years later she was able to resume her secretarial work and remained well for eight years. Three years prior to the time of the present study, she began to have pain in the left side of the chest and was admitted to the Bristol County Hospital where she has remained since. She had constant pain and cough, and occasionally haemoptysis. There was improvement in the cough and expectoration, but the pain in the left chest became worse and there were frequent elevations of temperature. Acid-fast organisms were found in the sputum on one occasion shortly after admission but none were found afterward. The physical examination was not remarkable except for the chest findings. There was limited expansion on the left side. A pleural friction rub could be heard over the greater portion of the left lower chest, and coarse râles were present posteriorly and inferiorly. The entire right side and the left apex were clear. There was no cyanosis and only slight clubbing of the finger-tips. Roentgenograms made from time to time varied little in appearance, and closely resembled those seen in case 1. The left lung field was entirely clear except for some cloudiness at the costophrenic angle. The right lung field was, by contrast, considerably denser than the left, as was also the hilum shadow. The peribronchial markings seemed intensified on the right (figure 2). Bronchoscopic examination by Dr. W. B. Hoover showed a narrowing of the left lower main bronchus. An injection of lipiodol outlined well the left bronchial tree. The primary upper left bronchus was displaced inferiorly and the three subdivisions of the upper left bronchus were distributed to the lung occupying the entire left hemithorax, except for a small area behind the heart shadow. A stenosis of the left lower bronchus could be seen with saccular dilatation in the smaller divisions (figures 3 and 4c). A lateral roentgenogram demonstrated a high position of the posterior leaf with flattening of the dome (figure 4d). A diagnosis of an atelectatic bronchiectatic left lower lobe was made.

A third case of bronchiectasis with a completely collapsed left lower lobe, which also illustrates the X-ray appearance of the lung fields in the uninvolved portions of the chest in such cases, has been studied. X-rays were taken at an early stage, just as the collapse was developing and before the upper lobe had become compensatively expanded, and nine months later, at which time the mediastinum had shifted back to its normal position and the uninvolved lobe had expanded to fill the entire hemithorax.

3: A man, aged twenty-six years, was seen in the Clinic because of symptoms of severe primary hyperthyroidism. While being prepared for operation, acute respiratory symptoms developed, with fever, cough, dyspnoea and cyanosis.

FIG. 2. Roentgenogram in case 2 showing left lower atelectatic bronchiectasis. Note the contrast in the density of the lung field on the two sides. The heart shadow obscures a shrunken bronchiectatic lobe. The left upper lobe has become distended to fill the entire left hemithorax. Because of the difference in density of the lung markings on the two sides, a first glance at such a roentgenogram might lead one to suspect an infection in the right lung. Compare relative position of right and left diaphragms in this X-ray with lateral view as shown in fig. 4D.

FIG. 3. Roentgenogram after lipiodol injection in case 2 showing bronchiectasis of left lower bronchi as cardiac shadow (retouched). Note saccular dilatation in left lower main bronchus in same area as cardiac shadow: a, b, c, represent the three secondary divisions of the left upper bronchus. Notice how they are branched out to be distributed to the left upper lobe which completely fills the lung field on the left side.

A bedside roentgenogram showed the heart to be displaced markedly toward the left (figure 5). There was a dense triangular shadow behind the heart, with its apex pointing toward the left hilum, and the lateral border of the density curving downward and laterally horizontal to, but inside of the heart shadow. The density of the left upper lobe was identical with that of the right lobe. A diagnosis of complete atelectasis of the left lower lobe was made. The acute symptoms subsided within a week, and later the patient successfully withstood a thyroidectomy. All the respiratory symptoms cleared up and at the time of discharge there were no signs in the chest except at the left base posteriorly. Nine months later, the patient was reëxamined. Diminished expansion, dulness, and râles in the left posterior chest were noted. A roentgenogram at this time showed the heart in its normal position, the same dense triangular shadow behind the heart, but the lung field on the left was only half as dense as that on the right (figure 6). The hilum shadow and peribronchial markings were also less in evidence. A lipiodol injection outlined the tracheobronchial tree well and demonstrated a bronchiectatic and collapsed

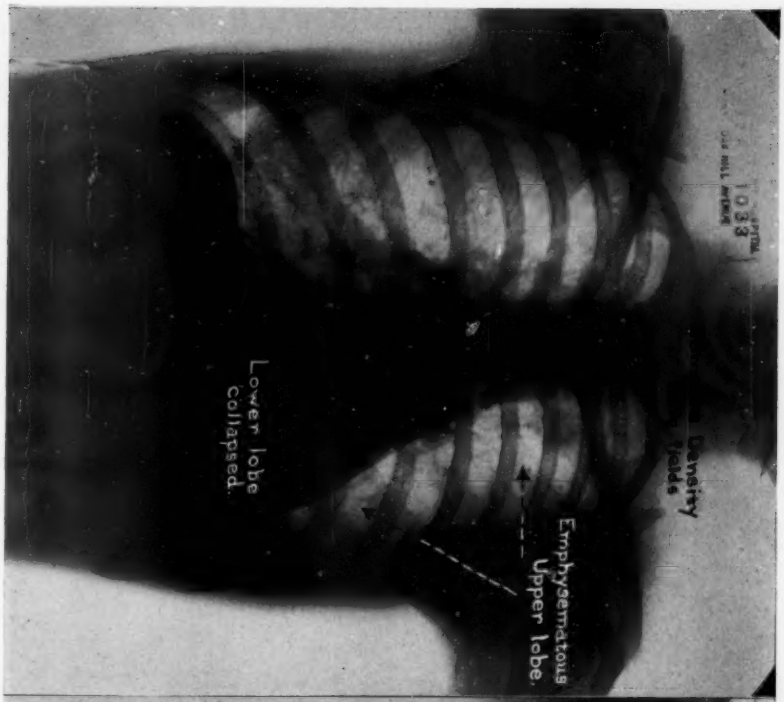
Dense fields
Emphysematous Upper lobe.
Lower lobe collapsed.

FIG. 2

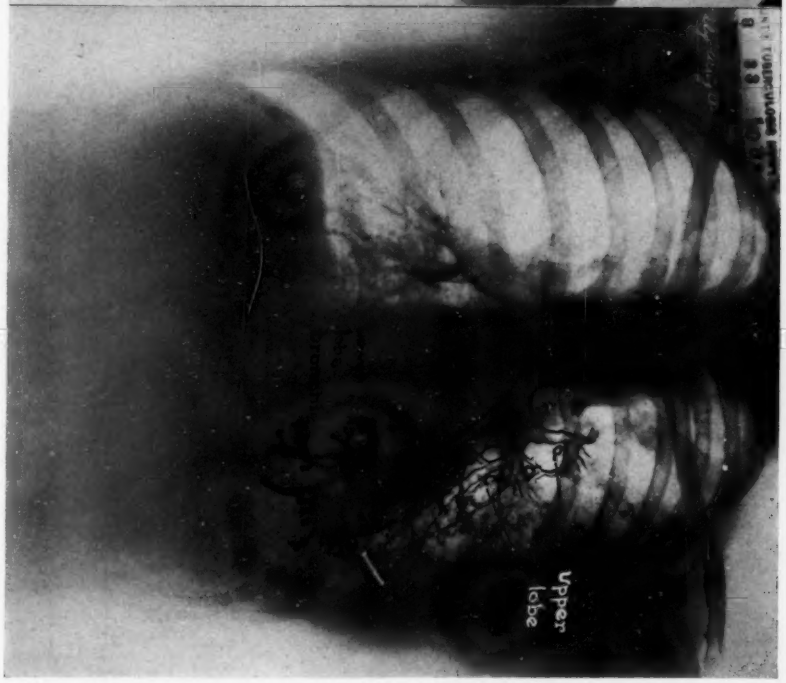
Upper lobe

FIG. 3

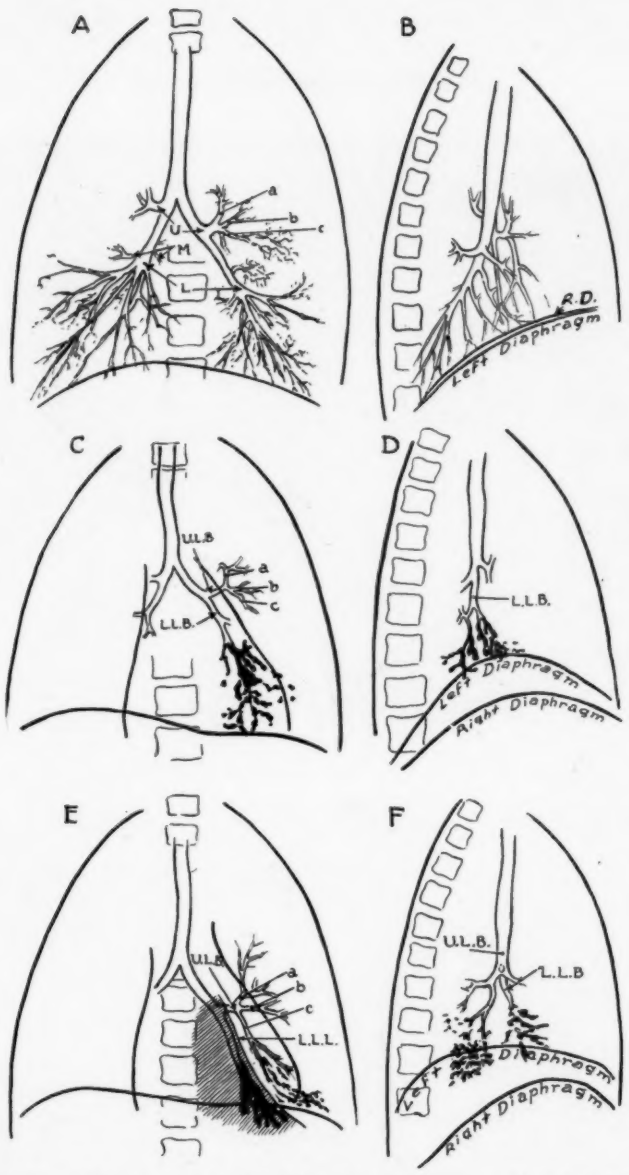

FIG. 4. Diagrams of bronchi reproduced from roentgenograms after lipiodol instillation to show normal and abnormal positions of their main divisions.

A: tracing from P–A X-ray in normal subject. Note position of left upper secondary divisions as indicated by a, b and c. Note wide distribution of lower bronchi.

B: tracing from lateral roentgenogram showing position of lower bronchus and normal relationship of the two leaves of the diaphragm.

C & D: tracings from case 2 showing distribution of upper and lower left bronchi. Note shadow of lower-lobe bronchus to be well within the cardiac shadow. Lateral view shows elevation of left diaphragm indicating reduction in size of overlying lobe.

E & F: tracings from case 3. Note secondary divisions of left upper bronchus (a, b and c) are displaced downward and are widened in their branching to be distributed to the entire left hemithorax. The lateral view shows marked elevation of the posterior leaf of the diaphragm which in turn indicates a marked reduction in volume of the overlying lung.

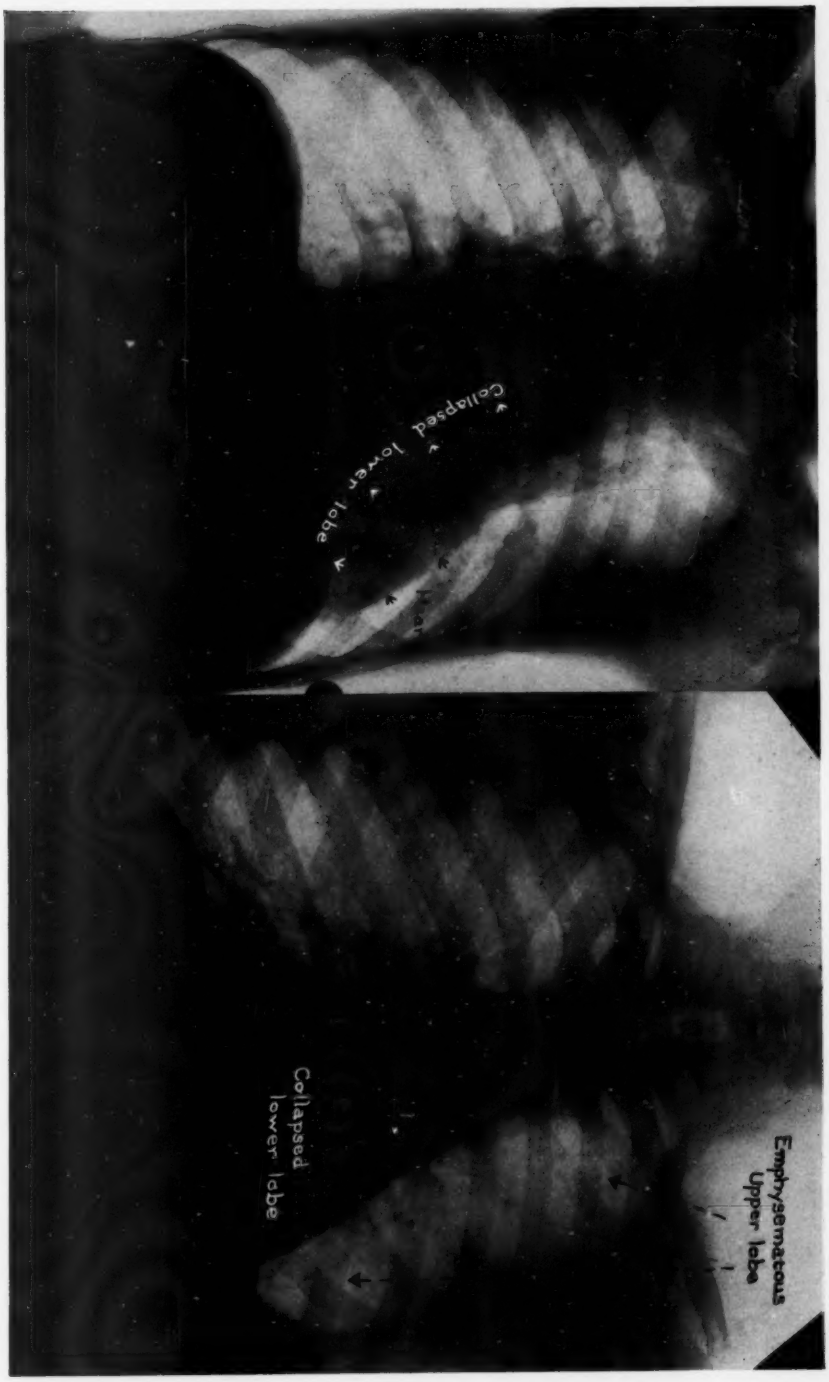
Collapsed lower lobe

FIG. 5

Emphysematous Upper lobe
Collapsed lower lobe

FIG. 6

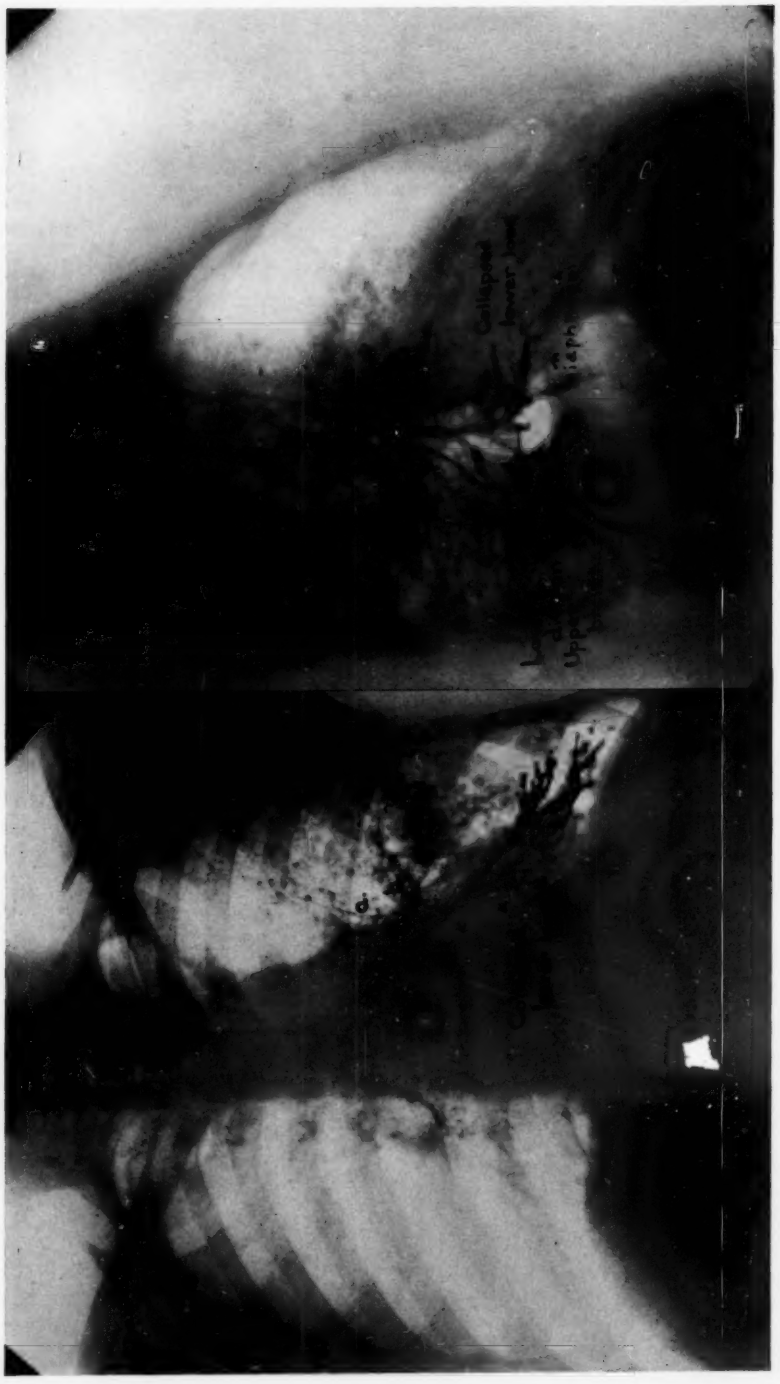

FIG. 8

FIG. 7

lower lobe. The three secondary bronchi of the upper left bronchus were spread out to be distributed to all parts of the lung in the left hemithorax (figures 7 and 8). The right bronchi were normal. A lateral roentgenogram revealed a high position of the posterior leaf of the diaphragm.

The course of events in this third case was interpreted as follows: An acute inflammatory process took place in the left lower lobe, with atelectasis of the lobe. At the time the bedside roentgenogram was taken in the early

FIG. 5. Roentgenogram in case 3 in an early stage of development of a complete atelectasis of the left lower lobe. Notice the swing of the heart and mediastinum to the left. Notice the similarity in the density of the lung marking on the two sides. At the time this study was made, the left upper lobe had not become compensatively emphysematous and therefore the density of the lung fields are about the same. In order for the contents of the thorax to adjust themselves to a reduction in total lung volume as a result of a collapse of the left lower lobe, there occurred an elevation of the diaphragm and a swing of the heart and mediastinum to the left side. This is the classical picture of mediastinal shift seen in postoperative massive atelectasis when one lobe is involved.

FIG. 6. Roentgenogram in case 3 nine months after development of collapse of left lower lobe. Compare this study with that made at the time of collapse, as shown in fig. 5. Now the heart is in its normal position. The lung field on the left side is clearer than the lung field on the right. Irrespective of the fact that the cardiac shadow obscures the hilum shadow, there is a definite difference in the intensity of the lung markings. It is this definite difference in the lung markings that should call attention in the plain film to the possibility of a collapsed left lower lobe. A very dense triangular shadow can be seen behind the heart shadow which represents the collapsed lobe.

FIG. 7. Roentgenogram in case 3 after lipiodol injection. This study reveals a completely collapsed and atelectatic left lower lobe well within the limits of the cardiac shadow. The three secondary divisions of the left upper bronchus are seen widely branching to be distributed to a distended left upper lobe. Some of the branches of the most inferior secondary division of the left upper lobe bronchus are dilated.

FIG. 8. Lateral roentgenogram in case 3. Note the extensive distribution of the bronchi of the left upper lobe. The left lower-lobe bronchus occupies a small area in the central and inferior portions of the chest. The posterior leaf of the left diaphragm is as high as the dome anteriorly. This marked elevation indicates a reduction in size of the lung above. Compare relative position of diaphragmatic leaves in lateral view and in P–A view, fig. 6, which illustrates value of lateral exposure.

stage of collapse there was a shift of the heart to the left, to take up the space resulting from the diminution in size of the left lower lobe. The density of the peripheral lung markings in the roentgenogram was equal to those on the right side because at this time some compensatory expansion of the left upper lobe had not taken place. In other words, the shift of the heart to the left had taken care of the decreased lung volume on the left, so that there was no need for a compensatory emphysema of the left upper lobe. In the roentgenogram taken nine months later the collapse of the left lower lobe was still

evident. The heart had returned to its normal position and the left upper lobe had become emphysematous, that is, taking the place of both lobes in the left hemithorax.

COMMENT

In the examination of the plain X-ray film in the first two reported cases, a marked difference in the density of the right and left lung fields was the most obvious abnormality. In both, the relative increase in density of the right lung field over the left at first lateralized the trouble in the right chest. Subsequent study in both cases demonstrated that the difference in the lung density had been produced by a compensatory distention of the left upper lobe which was a response to a shrinkage of the left lower lobe. In both cases, the shadow cast by the infected and shrunken lobe was obscured by the heart shadow. In both cases, the shadow of the dome of the diaphragm on the involved side, as seen in the P-A view, was in its normal position. Lateral X-ray views, however, showed marked elevation of the posterior leaf in each case.

In the third case reported, a shrinkage of the left lower lobe produced the typical X-ray appearance of an atelectatic lobe, inasmuch as the shadow was dense enough to be seen through the heart shadow. In this case, the secondary effects—a distention of the upper lobe and elevation of the posterior leaf of the diaphragm—were also seen.

These three cases illustrate, therefore, that evidence of bronchiectasis, affecting the left lower lobe may be seen in the plain X-ray film as secondary effects produced in the upper lobes. These secondary effects are revealed in the plain roentgenogram as a difference in density of the lung fields (indicating distention of the upper lobe on the affected side) and as an inequality in the position of the diaphragm best seen in the lateral roentgenogram. When such changes are seen in the ordinary P-A and lateral views, by inference an atelectatic bronchiectasis of the lower lobe should be suspected. It is not always necessary, therefore, to visualize an involved lobe behind the heart shadow.

Undoubtedly, there are many similar cases, in sanatoria and elsewhere, which have cough, expectoration, occasional haemoptysis, negative sputum, and roentgenograms which are inconclusive. A close study of the plain X-ray may reveal changes which are indicative of a shrunken bronchiectatic lobe behind the heart shadow. The investigation then can be supplemented by bronchoscopy and bronchography to confirm the diagnosis.

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A NEW OPERATING THORACOSCOPE

HENRY I. GOODMAN[1]

The increasing use and wider indications for the use of artificial pneumothorax in the treatment of pulmonary tuberculosis testifies to its therapeutic importance. Many times the efficiency of a therapeutic pneumothorax is impaired by adhesions which prevent an adequate collapse. By gradually increasing the intrapleural pressure some of the more delicate adhesions have been stretched or even torn. This method is not always successful and carries with it certain dangers.

Twenty years ago, Jacobaeus first successfully divided intrapleural adhesions under vision, using the actual cautery. The method presented certain difficulties. It was necessary to make two punctures in the chest-wall. It was difficult to coördinate the movements of the cautery with thoracoscopic vision. Most important, the actual cautery was used and haemostasis was not always effective. However, sufficient interest has been aroused in this procedure so that other instruments from time to time have been introduced, each overcoming some disadvantages in previous instruments.

Unverricht in 1925 improved the Jacobaeus instrument to such an extent that the method became popularized by his instrument. Then direct-vision instruments were introduced by Head and Mascher in 1929. Finally, a thoracoscope was introduced with an improved optical system on the order of a cystoscope which operated through a single puncture of the chest-wall. During the past five years instruments of this type have been introduced by Davidson (1929), Chandler (1930), Howe and Kalk, and Cutler. At best this operation is not easy, but it certainly is easier to perform the operation with a single-unit instrument. The adaptation of the high-frequency current to the cutting of adhesions by first coagulating and then cutting them has been of the utmost importance. Chandler, Davidson, Maendl, and Matson are using the high frequency current to cut adhesions. Maurer uses a combination of diathermy and galvanocautery. There can be little ques-

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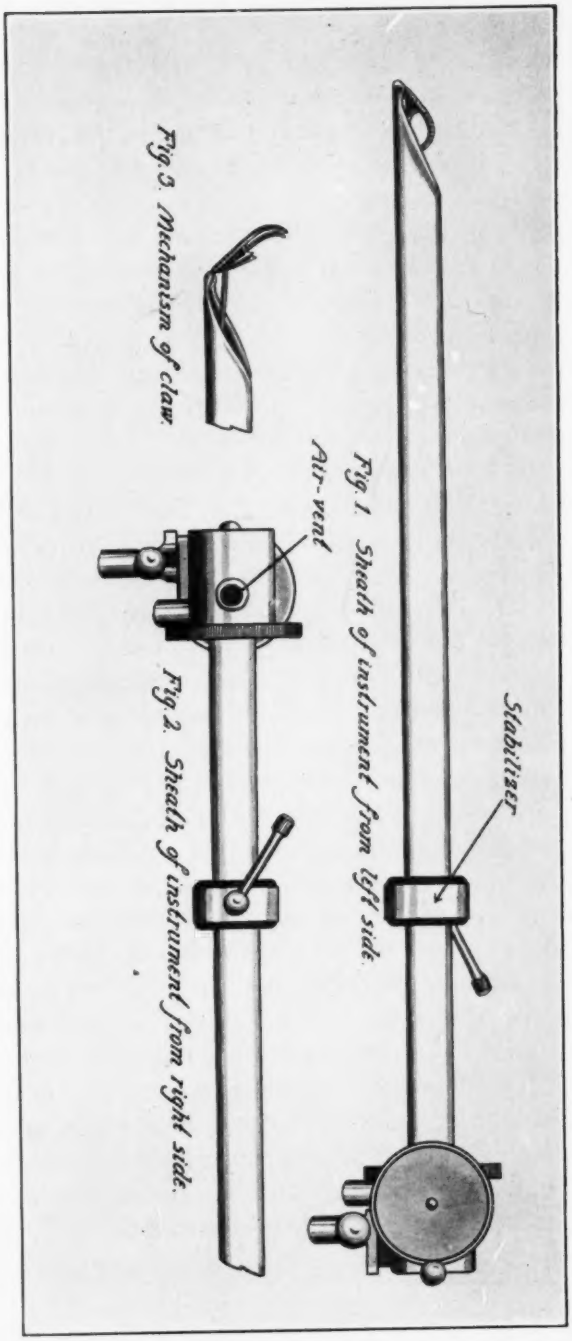

Fig. 1. Sheath of instrument from left side.

Fig. 2. Sheath of instrument from right side.

Fig. 3. Mechanism of claw.

tion that electrosurgery is superior to the actual cautery for this type of operation.

The instrument about to be described offers, the author believes, advantages not found in other instruments. It consists of two parts, a special type of cannula and an operating unit. The cannula is oval-shaped, about 24 F obliquely cut off at one end and blunted. This end has a door-like arrangement which presents a double claw when opened by a turn of the knob after its introduction into the pleural cavity. This claw can be lowered to make an angle at maximum of about 135 degrees with the cannula. On the opposite side of the knob, a hand-bulb can be connected to blow away steam or smoke. The operating unit consists of a McCarthy fore-oblique vision telescope and an electrode (active) which moves forward and backward on a rack and pinion arrangement.

The cannula is introduced through a half-inch incision made with a scalpel through the skin and pleura. The blunted end of the cannula prevents any injury to the underlying structures on its sudden introduction into the pleural cavity. The operating unit is then inserted into the cannula. Meanwhile, the indifferent electrode has been secured to the patient. When the adhesion has been found, a turn of the knob turns down the claw which is very easily manipulated to engage the adhesion, which can then be lifted and explored. Under vision, the active electrode is now brought in contact with the adhesion and coagulation of the adhesion is begun. After sufficient coagulation has taken place and by only changing the type of current the band is cut.

There are two important features in this instrument. By engaging an adhesion which is running parallel to the instrument along the side of the serrated surface of the claw and then slightly rotating the instrument, the operator brings the adhesion within the range of the active electrode. This feature, to be able to cut an adhesion running parallel to the instrument, cannot be sufficiently overemphasized for a single-puncture instrument. On occasion, the adhesion may be short and broad. To cut this adhesion, the claw is turned back into the instrument and the active electrode is thrust out past the cleft in the claw and the whole instrument rotated 180 degrees. By means of the projecting electrode, such bands can be coagulated and peeled from the chest-wall. This is the important second feature of the instrument. Almost every instrument will cut adhesions running at right angles or nearly so to the

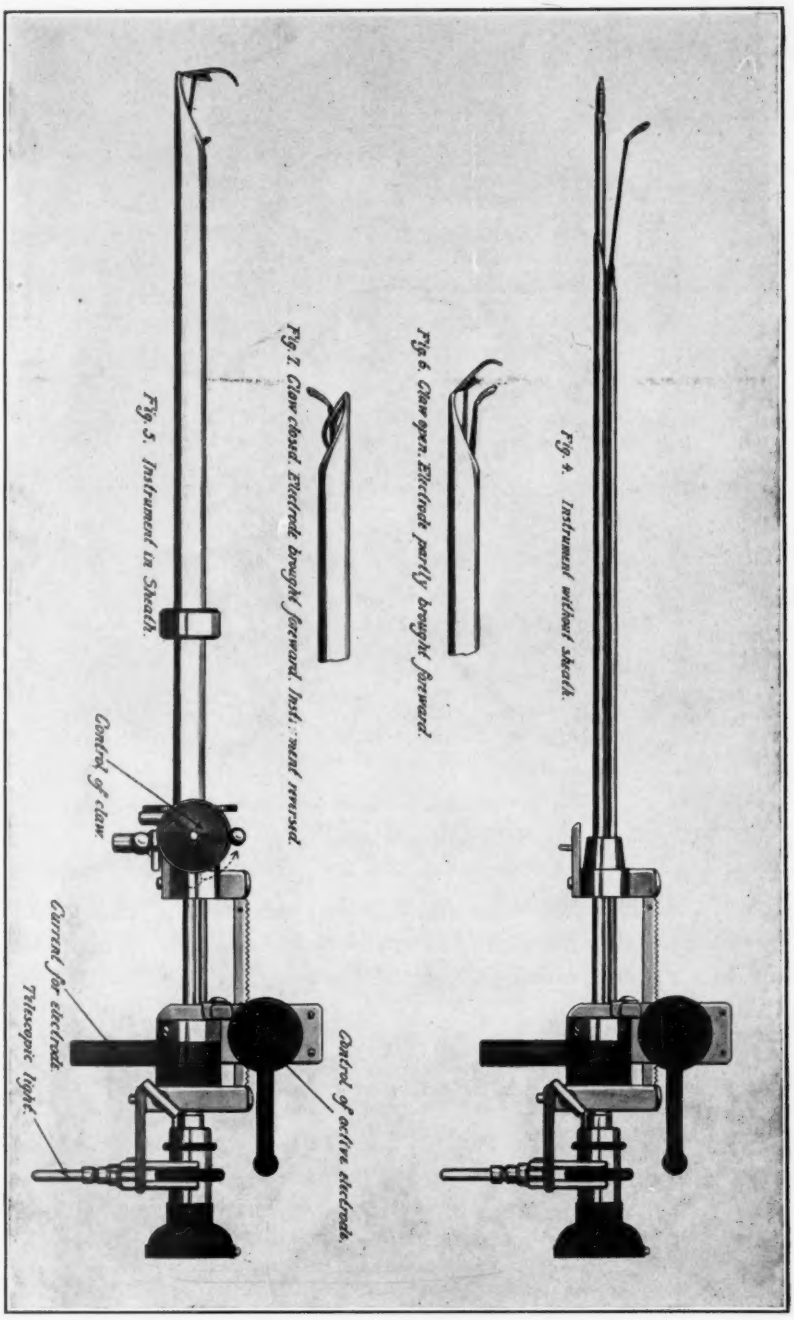
Fig. 4. Instrument without sheath.
Fig. 5. Instrument in Sheath.
Control of claw
Barrel for electrode
Telescopic light
Control of active electrode
Fig. 6. Claw open. Electrode partly brought forward.
Fig. 7. Claw closed. Electrode brought forward. Instrument reversed.

instrument. The author believes that the above features present decided advantages for the instrument.

Fig. 8.
Instrument parallel to adhesion.

Fig. 9.
Instrument at right angles to adhesion.

Fig. 10.
Instrument at right angles to adhesion.

Fig. 11.
Instrument reversed – claw closed – electrode cutting thick band.

To date, the instrument has been tried in two cases. There can be no conclusions possible from two cases, unfortunately; but the adaptability and the ease of manipulation of the instrument were readily demonstrated.

The author wishes to acknowledge his indebtedness to the American Cystoscope Makers, Inc., for their kind coöperation in the development of this instrument.

THE QUESTION OF WHEN ARTIFICIAL PNEUMOTHORAX SHOULD BE DISCONTINUED

PAUL DUFAULT[1] AND ARMAND LAROCHE[1]

The men doing pneumothorax therapy are more than ever puzzled, and justly so, when facing the question of permitting the reëxpansion of a collapsed lung. The problem is arising more and more frequently and its proper solution is of greater import, for the simple reason that an improved technique and a more scientific management of our pneumothoraces have enabled us to continue them much longer.

Only a few years ago, the question was, in most instances, settled of itself. A progressive obliteration of the pleural space or a large effusion forced out the hand of the physician after a year or two. The collapses that he did not lose, he usually abandoned voluntarily toward the beginning or middle of the third year, feeling that he had accomplished as much as the majority of phthisiologists and had done all he could.

However, times have changed. The wider practice of intrapleural pneumolysis, the removal of fluid and its replacement by air, and antiobliterative oleothorax have added considerably to the value of our collapses. They are not only more complete and more effective but they are also more durable. The physician is no longer satisfied in accepting the dictates of complications; he tries to master them, and he usually succeeds.

The time comes, after two, three, or more years of treatment, when both physician and patient begin to wonder: How long should the refills be continued?

Because of our lack of experience and of careful follow-ups, answers have been rather theoretical and vague, and not always in agreement. Patients must of necessity be individualized. It seems, however, that some general conclusion could be drawn from a careful study of our old cases. In the light of a small but representative survey, let us review the situation and summarize the pros and cons.

1: Abandonment of pneumothorax is advocated first of all to prevent the permanent loss of function which might result from a long-standing

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state of collapse. Very captious, this argument does not stand after a moment of reflection. It is a well-accepted fact that the healthy areas remain practically unchanged and readily resume their function whenever allowed to unfold, regardless of the duration of their immobilization. Their elasticity has not been impaired. The diseased tissues alone are incapable of reëxpansion, provided sufficient proliferative organization has taken place. This is well illustrated in figures 1, 2, 3, 4, 5 and 6. Cases have been reported as failing to reëxpand and as necessitating thoracoplasty. These are exceptional, and usually due to pachypleuritis, which is just as liable to appear during the first year of pneumothorax as later.

2: The inconvenience to the patient: This issue becomes pressing when he contemplates leaving the sanatorium. Where shall he have his refills? In some parts of the country, densely populated and well organized in the field of tuberculosis, he can secure them within a reasonable distance of his home. In others, rural sections especially, removed from large centres, there is no alternative other than to stay in the sanatorium or to give up the treatment. Travelling a hundred miles is practically out of the question. The fatigue resulting from such trips would be sufficient to make it prohibitive, not to mention the expense incurred. In some circles there seems to be a tendency to discontinue pneumothorax early and to substitute phrenicectomy in order to hasten the date of discharge. Such a concession to the pressure of long waiting-lists does not seem warranted. Patients do not have to remain in the sanatorium during the whole period of pneumothorax, but the necessary provision should be made for them to continue their refills as long as necessary after discharge. The National Tuberculosis Association has felt the need of a nation-wide network of refill stations in order to facilitate the continuation of collapse treatment under proper conditions and in qualified hands, and its organization is now in progress. It will be a godsend to numerous tuberculous individuals who have to shorten their treatment and put their life in jeopardy because of lacking facilities in this field.

3: The expense: Unless obtained from a state or county sanatorium or from a free clinic, the refills are somewhat costly, and the prospect of continuing them for several years is not a cheerful one to the patient of moderate or small means. This can always be arranged somehow. It should not be forgotten that the cost of illness and invalidism is still a greater burden to the patient or to his community than that of treatment. One or the other has to pay.

FIG. 1 FIG. 2 FIG. 3

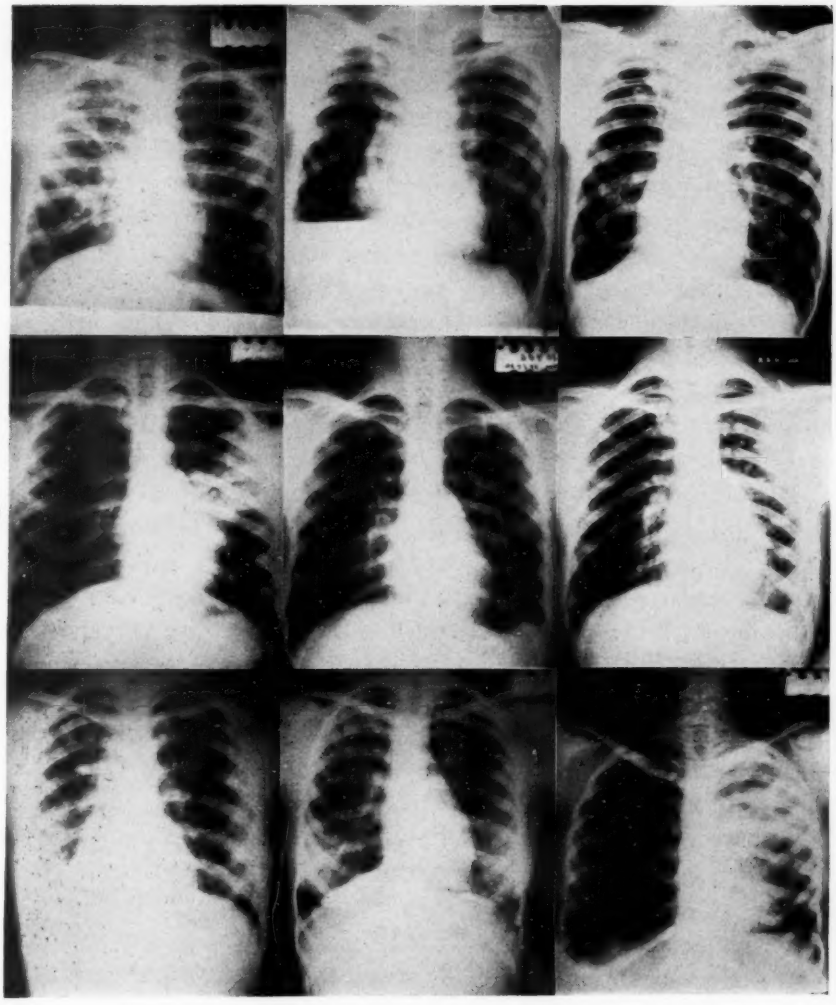

FIG. 4 FIG. 6

FIG. 7 FIG. 8 FIG. 9

FIG. 1. July, 1928. Note amount of pathological involvement.

FIG. 2. Same case. Note amount of collapse kept for 3½ years.

FIG. 3. February, 1934. Same case. Lung allowed to come out partially. Besides a few calcifications and an area of fibrosis in the first interspace the lung field is clear and reëxpands easily.

FIG. 4. September, 1927. Cavity near hilum. Large area of exudation.

FIG. 5. Same case as in figure 4. A 90 per cent degree of collapse was maintained for 7 years. Film was taken just before refill.

FIG. 6. Same case, January, 1934. Lung reëxpanded. Parenchyma clear except for a few calcifications and pachypleuritis in axilla.

FIG. 7. W. B., age 21. May, 1927.

FIG. 8. H. S., age 19. August, 1926.

FIG. 9. O. G., age 18. September, 1925.

4: The danger of embolism, of pleural shock, or of infection must be mentioned. In old cases, however, it is remote. Purulent pleurisies of septic origin have been reported after the seventh year. In some exceptional cases, also, refills are followed by rather severe reactions characterized by general malaise and fever as high as 100° to 101° even after years of treatment. The patient whose films are shown in figures 4, 5 and 6 was an example of this. Such instances are exceptional and naturally resort to the attending physician's judgment.

Let us consider now the eventualities in store for the reëxpanded lung:

It is hardly necessary to recall the relativity of the cure obtained in tuberculosis. The sad procession of quiescent and even arrested cases incessantly retracing their weary steps toward our sanatoria is an eloquent demonstration of its fragility. How acutely those repeaters realize the cruel truthfulness of the old saying: "Once tuberculous, always tuberculous!" The old invader of their childhood or adolescence may be slumbering for years but it is seldom dead. Being very humanly inclined to forget and to overdo during the lulls, the patients are often partly responsible in bringing upon themselves the storms that they have to weather, but the facts remain to be faced. Exacerbations may vary greatly in degree and severity; they may assume the characteristics of a grippe, of a simple cold, or even pass unnoticed except for a mild sensation of fatigue or a slight haemoptysis without any untoward effect, but they are all manifestations of the same continuous process. That some of those patients carry on indefinitely and even reach old age does not impair this observation in any way.

Complete excision of the pathological process, were it possible, would be the ideal solution. The time may still come when an improved surgical technique will allow such a procedure. The rapid progress made in thoracic surgery during the past few years has brought this new realm into view, and what used to be a visionary idea has become a logical hope.

In the meantime, the best that we can do is to keep those diseased areas under control by artificial collapse and to make such a collapse as complete, as effective, and as lasting as possible. Let us not forget that fibrotic bands and calcified nodules, which are the final stages of healing throughout the necrotic areas, are only walling-in the bacilli and are still, after all, undesirable elements. At their best, they can be nothing but scars, of no use whatever to the function of ventilation. Their untimely release is fraught with danger. This feeling is being implicitly expressed every time that a phrenic exairesis or thoracoplasty is performed with

the view of adding to the duration of a pneumothorax. Is a thoracoplasty anything but a partial and permanent collapse?

5: Length of treatment: The condition of the lung before collapse is one of the deciding factors when reëxpansion is considered. A simple exudation, a recent infiltration without any visible cavities, are expected to regress readily and to be absorbed in a relatively short time. It is customary to say that such lesions clear up with a simple phrenicectomy or even on bed-rest alone. There is no doubt that they often do. But who knows? And if, after a few months, very little or nothing has been accomplished, precious time has been wasted. On the other hand, a good pneumothorax will almost always turn the tables in favor of the patient. It will stop a progressive lesion. It will hasten the regression of an indifferent process and also hasten an otherwise slow absorption. An objection often raised to the establishment of pneumothorax in early lesions is that it should be kept in reserve in case of future breakdowns. Is not this an admission of the precariousness and uncertainty of the patient's condition without it? Is it not another proof that, subconsciously, we all fear relapses? Then why not institute a collapse from the beginning, and hold it as long as we do not feel satisfied that complete absorption has taken place?

When will that be? There are many divergent opinions, but the leading authorities seem to agree that, with the type of lesions just described, two to three years of collapse, counting from the time the sputum turned negative, should be sufficient. This is the minimum duration of pneumothorax, with the exception of bilateral cases when the question is altogether different. It is granted that durable results have been obtained in a shorter time, but their percentage is relatively small.

In case of an older, fibrocaseous lesion, with thick-wall cavities, a minimum of five to seven years is required. That period is not arbitrarily set. It is based on the slow process of healing in tuberculosis. It is also substantiated by surveys of reëxpanded cases followed from two to ten years.

A thesis published in 1932 by deWeck is particularly interesting. Out of 51 cases treated by pneumothorax and observed from 2 to 19 years after reëxpansion, he reports as follows:

Collapsed less than a year: 3 cases: 6%	
Cure maintained	66%
Old lesion reactivated	34%
Extension to opposite lung	0

Collapsed from 1 to 2 years: 7 cases: 14%	
Cure maintained	100%
Old lesion reactivated	0
Extension to opposite lung	0
Collapsed from 2 to 3 years: 12 cases: 24%	
Cure maintained	75%
Old lesion reactivated	16%
Extension to opposite lung	9%
Collapsed from 3 to 4 years: 14 cases: 27%	
Cure maintained	78%
Old lesion reactivated	14%
Extension to opposite lung	8%
Collapsed from 4 to 7 years: 14 cases: 27%	
Cure maintained	85%
Old lesion reactivated	7%
Extension to opposite lung	7%
Collapsed from 8 to 10 years: 1 case: 2%	
Cure maintained	100%

It is unfortunate that the author did not classify his cases according to the nature of their lesions. The striking feature of his table is the constant progression in the percentage of cures increasing with the number of years during which the pneumothorax was maintained and the constant decrease of breakdowns at the site of the old lesion.

Out of 51 cases having a "satisfactory and effective collapse," optionally discontinued before two years of treatment (except 5 extending to three and four years), Peters reports 32 per cent of relapses and 12 per cent of deaths, within a few years. Is not this a far too large percentage of breakdowns?

Our survey comprises 65 cases of clinically effective pneumothoraces. Every patient, starting with demonstrable cavities and positive sputum, had gained weight, and was afebrile and bacilli-free at the end of his treatment. All but 11 were reëxpanded within the past 5 years. In most instances, progressive obliteration was responsible for the reëxpansion. (For several years now, we have been resorting to oleothorax with fair success in this type of cases.)

The first series of figures shows the results obtained according to the duration of collapse, and the second one according to the patient's age.

One year or less: 18 cases: 27.7%	*cases*	*per cent*
Cure maintained	6	33.3
Still taking bed treatment	4	
Relapsed	8	66.6

	cases	per cent
From 1 to 2 years: 19 cases: 29.3%		
Cure maintained	11	58.0
Still taking bed treatment	0	
Relapsed	8	42.0
From 2 to 3 years: 15 cases: 23%		
Cure maintained	7	47.0
Still taking bed treatment	3	
Relapsed	5	53.0
Over 3 years: 13 cases: 20%		
Cure maintained	11	84.6
Still taking bed treatment	1	
Relapsed	1	15.4
Total of all cases: 65 cases		
Cure maintained	35	53.8
Still taking bed treatment	8	
Relapsed	22	46.2

	cases	per cent
Under 21: 15 cases: 23.1%		
Cure maintained	6	40.0
Still taking bed treatment	1	
Relapsed	8	60.0
21 to 25: 27 cases: 41.5%		
Cure maintained	15	55.6
Still taking bed treatment	3	
Relapsed	9	44.4
26 to 30: 10 cases: 15.4%		
Cure maintained	6	60.0
Still taking bed treatment	1	
Relapsed	3	40.0
Over 30: 13 cases: 20.0%		
Cure maintained	8	61.5
Still taking bed treatment	3	
Relapsed	2	38.5

The percentages of persisting cures, increasing with the length of time during which the collapse was maintained and with the age of the patients at the beginning of their illness, are very striking. Striking, also, are the inversely decreasing ratios of breakdowns and deaths (among the relapsed cases 9 are dead). It is only logical to assume that, of this latter group, many would be alive and well to-day, had their collapse been maintained longer. This contention is strengthened by the fact that half a dozen of the well cases had their disappearing pneumothorax supplemented by a phrenicectomy, and that four patients of the other group already showing signs of relapse were caught in time, had a thoracoplasty, regained the healthy status which was theirs at the end of their pneumothorax, and are still maintaining it.

Now for a few individual examples:

W. B., age 21, whose admission film (May, 1927) is shown in figure 7. Discharged October 14, 1928, she went through training school, graduated and is doing nursing duty at present. Pneumothorax since May, 1927.

H. S., after seven months of treatment left the sanatorium at the age of 17, a quiescent case, and came back two years later with lungs that may be seen in figure 8. Discharged June 23, 1928, she trained and graduated as a nurse, and is working every day. Pneumothorax since August, 1926.

O. G., came to us in September, 1925, at the age of 18, admission film figure 9. After leaving the sanatorium, November 23, 1927, she could complete her education and finally graduated from an art-school. She is perfectly well to-day. Pneumothorax since September, 1925.

These patients might have done well with shorter treatment. But who would have cared to take a chance? Would it have been wise to abandon those young girls to their fate at the ages of 24, 22, and 21, respectively, allowing three years of collapse, which is still above the average duration of pneumothorax, and to let them travel unprotected through the critical period of their twenties? Which one of us would, to no advantage, run such a risk?

A good pneumothorax, solidly built on a reasonable period of bed-rest, has helped them to win their fight against tremendous odds. We wish to protest at this point against the pernicious practice of presenting the pneumothorax to the patients as a substitution for bed-rest and as a means of shortening the treatment. It is starting them on the wrong track. Such short-cuts lead rapidly and almost infallibly to disaster.

CONCLUSIONS

We do not pretend to have brought up anything new. We have simply tried, in the light of our experience and study, to answer the often repeated query: "When should pneumothorax be discontinued?"

We believe that the guiding factors in deciding reëxpansion are the condition of the lung before collapse, the nature of the lesions more than their extension, and the age of the patient. We are convinced that the objections to the prolongation of the pneumothorax are unimportant in comparison with the risks incurred by its undue abbreviation; that the obstacles to its continuation are surmountable; and that its premature discontinuance compromises, in too great a proportion of cases, the results that may justifiably be expected from it.

HYPERSENSITIVITY TO NOVOCAINE IN ARTIFICIAL-PNEUMOTHORAX THERAPY

WILLIAM M. MacKAY[1]

In the treatment of pulmonary tuberculosis by artificial pneumothorax we have noted occasionally slight reactions following a refill which we considered of no particular significance in that they caused the patient but little discomfort and lasted but a few hours.

One or more of the following symptoms have been complained of: chest discomfort, fever, anorexia, aching sensation throughout the body, and general malaise.

If we had stopped to analyze the cause of these after-effects we would probably have attributed them to the treatment rather than to the local anaesthetic used to anaesthetize the skin and other tissues prior to inserting the pneumothorax needle.

In looking over a period of years, two cases stand out particularly which were always followed by a reaction. The first patient always complained of pain in the pneumothorax side the day following a refill and attributed it to the novocaine used as a local anaesthetic. The use of novocaine was discontinued and the patient remained free from pain. In the second case, for two days following a refill the patient complained of anorexia and nausea, severe aching sensation, and general malaise. It was suggested to her that the novocaine might be the cause of her symptoms and without its use she might avoid them, but she preferred to receive the treatment with the use of novocaine rather than without. Varying the amount of the refill in this case did not influence the result and the patient continued to spend most of her week-ends in bed following a refill.

Other cases are recalled in which the patient has complained of anorexia and general malaise. There are probably many cases in which the patient has noticed some unpleasant after-effect but has not reported it to the attending physician.

Case Report

M. S., female, age 25, married, admitted to Middlesex County Sanatorium, October 10, 1933. Family history negative for tuberculosis. No history of

[1]Middlesex County Sanatorium, Waltham, Massachusetts.

exposure to tuberculosis. *Past History:* Measles and diphtheria during childhood, frequent colds for the past few years. *Present Illness:* Onset indefinite. Five years prior to admission to sanatorium patient went to general hospital to have tonsils removed but, as she had a cold at the time, operation was postponed pending investigation of her chest condition. Chest X-ray suggested lesion in lungs. Patient states that she was re-X-rayed a few weeks later and told that chest was clear. Tonsils not removed. Patient remained well until August, 1932, when she went to hospital on account of pregnancy. Following delivery she lost a lot of blood. She returned home but, as she continued flowing, was taken back to hospital for curettage. Remained in hospital for two weeks and then went to mother's home, where she rested until April, 1933. In April she returned to her own home and resumed her housework. Upper teeth removed at intervals in May, followed by bleeding from gums about two days after each extraction. In June patient complained of wheezy sensation in chest on waking in morning. Voice became husky and she suddenly lost her voice completely. About end of June she began to complain of tickling sensation in throat causing frequent cough. Consulted physician in July on account of cough and loss of voice. Chest, throat and sputum examined, following which diagnosis of pulmonary and laryngeal tuberculosis was made. Medicine prescribed and symptoms subsided, patient recovering use of voice, and cough apparently subsiding. Caught cold in August, resulting in recurrence of symptoms, but more severe than previously. A physician examined her throat, and patient states she was told that she had laryngitis for which she was given treatment by sprays. Later began to complain of "noises" in right lung. Since then has been subject to exacerbations of symptoms at intervals characterized by wheezing, loss of voice, cough, and expectoration. On August 13 returned to mother's home and took continuous bed-rest treatment. On admission to sanatorium stated that she had felt choked up for the past two weeks. Had slight sore throat, was coughing and raising moderate amount of mucopurulent sputum, found to be positive for tubercle bacilli. Appetite poor and patient subject to indigestion and constipation. Also complained of aching sensation along vertebral border of right scapula. Temperature ranging around 99°. Patient extremely nervous and easily agitated.

Physical Examination: General development fair, poorly nourished. Upper teeth missing and several lower teeth carious. Tonsils enlarged and spongy. Physical examination of chest showed nothing other than slightly diminished breath-sounds and few questionable deep-seated râles posteriorly above scapular spine on right. Laryngoscopic examination showed arytenoids slightly injected. Later examination showed swelling of arytenoids and interarytenoid space. X-ray examination showed pulmonary tuberculosis involving predominantly right upper lobe.

On December 26 artificial pneumothorax was induced on the right, resulting in selective collapse after a few refills, but rather limited in extent owing to the presence of adhesions. In the administration of the treatment 1 per cent novocaine was used for anaesthetizing the tissues prior to inserting the pneumothorax needle. A 19-gauge Luer needle was used. Patient was given refills at frequent intervals but at no time resorting to positive pressure and with no apparent discomfort immediately following the refills. However, it was noticed that she began to complain frequently of wheezing. Examination of chest showed numerous rhonchi in both lungs. It was felt that the patient was having an exacerbation of the symptoms complained of prior to admission to the sanatorium, and the symptoms and signs were suggestive of asthmatic bronchitis. On February 2, 1934, some time following a refill, patient had a severe attack, characterized chiefly by labored breathing, and relieved by a subcutaneous injection of adrenalin. The attack recurred the same night and was again relieved with adrenalin, the patient remaining fairly comfortable until the next pneumothorax refill. On February 9, about 45 minutes following a refill of 400 cc., patient had another severe reaction, characterized by labored breathing, a feeling of tightness in the mediastinal region, weak rapid pulse, and marked prostration. Was again given adrenalin but as no immediate relief was obtained, she was given a subcutaneous injection of morphine. Was then taken to operating room and 200 cc. of air were removed, although manometer reading was negative on inserting the needle. This was followed by gradual improvement, so that by noon she appeared quite comfortable. However, it was felt that the relief was obtained from the medication rather than removal of air.

Considering this case in retrospect, it now appears that the wheezing complained of since admission was partly due to, or at least aggravated by, novocaine and that the severe reactions noted following pneumothorax refills of February 2 and 9 were almost certainly due to novocaine, in that subsequent refills have not been followed by any reaction. Having come to this conclusion it was decided to continue the refills but without the use of a local anaesthetic. Accordingly, on February 16 patient was given refill of 200 cc. only, it having been decided to start with small refills and to step them up gradually. This refill was followed by no discomfort of any kind, the patient's condition remaining good and no medication being required during the day. Since then the patient has complained of wheezing at intervals independent of pneumothorax refills but with no marked weakness or other signs of prostration and the physical examination has shown the presence of numerous rhonchi throughout the lungs.

To digress from the main subject for a moment, the patient was questioned closely to see if any severe reactions had followed the extraction of her teeth. She stated that novocaine had been used but she was unable to recall that

there had been any unpleasant after-effects as the result of it. This suggests that the hypersensitiveness to novocaine may be of recent origin.

A month has now elapsed since the last severe reaction following pneumothorax therapy and the patient is still receiving pneumothorax refills at weekly intervals without the use of a local anaesthetic. It has been noted that she has complained much less of wheezing than formerly, although her general condition has not improved.

SUMMARY

A case is reported in which following the administration of artificial pneumothorax, using novocaine as a local anaesthetic, the patient developed a severe reaction characterized chiefly by labored breathing and marked prostration. In the light of subsequent events it seems reasonable to assume that the reaction was due to novocaine. The question is also raised as to whether certain unpleasant after-effects complained of by patients generally, who are receiving artificial pneumothorax treatment, may not be due to novocaine or similar products used in conjunction with the treatment rather than to the treatment *per se*.

APICAL LOCALIZATION OF PULMONARY TUBERCULOSIS

The Pulmonary Tissues as Excretory Organs for Tubercle Bacilli[1]

JEROME J. HURWICH AND GEORGE MILLES

Investigators in tuberculosis have for many years been searching for an explanation which would adequately account for the great frequency of apical tuberculosis (latent apical tuberculosis has been found in the lungs of one out of every five white adults (1)). Although many hypotheses have been presented, up to the present time no one has been universally accepted as an adequate explanation for the problem at hand. A great deal of confusion exists, as evidenced by the great number and variety of theories.

The question of the degree of aeration of the apices of the lungs has been raised time and again in discussions regarding the underlying factors responsible for apical predisposition to tuberculosis. Many of the investigators have presented evidence which tends to show that there is deficient aeration of the apices; others maintained that aeration of the apices is normal; still others have maintained that the apices are especially well aerated.

Freund (2), Hart (3), Birch-Hirschfeld (4), and others believed that there is impairment of aeration of the apices due to a stenosis of the upper thoracic aperture resulting from an early ossification and shortening of the first-rib cartilage; this stenosis of the upper thoracic aperture with its accompanying impaired aeration and nutrition was held to be the underlying factor in apical predisposition. Bacmeister (10) injected tubercle bacilli into rabbits in which he had previously produced an artificial stenosis of the upper thoracic aperture and obtained results which tended to substantiate the theories of Freund. Iwasaki (5) repeated these experiments of Bacmeister, and came to the conclusion that they could not be used as evidence in support of the Freundian theory. Furthermore Davies (6), Wolff-Eisner (7), Ulrici (8), and others have shown by anatomical and roentgen studies that neither the abnormal shortness nor the ossification of the first-rib cartilage predisposes to

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apical tuberculosis, since these abnormalities have been observed with equal frequency in individuals who have and who have not apical involvement. Freund also maintained that, when the ossified cartilage was fractured with the development of a false joint, there was a marked tendency for apical tuberculosis to clear up; he therefore advised operations on the first rib with the formation of a false joint as a method of treatment. This view was also disproved by Davies. Schmorl (9) drew attention to the existence of a groove on the posterior outer aspects of the apex of the lung caused by the pressure of the first rib, and showed that this was a common place for the development of tuberculosis. This was regarded by Freund as further evidence in support of his theory. Davies (6), however, regards this groove not as the result of abnormal shortness of the costal cartilage, but as probably the result of an emphysema. Birch-Hirschfeld (4) noted a deformity of the apical bronchus. which he regarded as the underlying factor in apical predisposition; this deformity was regarded by Schmorl as being due to pressure of the first rib,—the same as causing the furrow which he described.

Pottenger (11) also maintained that there was a deficient aeration of the apices, but held that this was due to a disproportion of the growth of the lungs in relation to the chest,—particularly emphasized in the upper thorax which is really flattening and narrowing in the growing child, with resulting increasing compression of the apices as the child grows to adulthood. The impaired aeration, the compression of the alveolar spaces, the accompanying impaired blood and lymph circulation,—all are factors, which, according to Pottenger, reduce the resistance of the apices to tuberculosis.

Campbell (13), one of the earliest to maintain that aeration of the apical tissues is deficient, writes as follows:

> The extreme apex in man being extra-thoracic . . . . on inspiration the intra-thoracic lung is under a pressure which is communicated to it by the soft parts covering it; this (residual alveolar) air meets the incoming air from the trachea and larger bronchi and the pressure becomes equalized. The result is that on inspiration only a small amount of air reaches the apex. Again on expiration the pressure on the apex being that of the atmosphere and hence less than that of the rest of the lung, the air rich in carbon dioxide and poor in oxygen is forced into it. From the above it follows that the contents of the apex are under the most unfavorable conditions for becoming aerated and the vitality of the tissues is lessened and hence their resisting power is lowered.

Beitzke (14), Penzoldt (15), Jaeger (16), and others maintained that the degree of aeration of the apices depends entirely on how the individual breathes: during quiet respiration there is, as in other parts of the lungs, an expansion of the apices with inspiration and collapse during expiration but the degree of expansion is less than that in other parts of the lungs; with stronger respiration the aeration of the apices is good; however, with forceful breathing, as in coughing, dyspnoea, etc., there is a complete reversal of the process in the apices: the apical tissues collapse during inspiration due to suction of the air from the alveolar spaces of the apex into the alveolar spaces of the lung parts below, and during expiration the forcing of air from the lower parts of the lungs into the apices results in expansion of the apices. The impaired aeration of the apices is held by Beitzke and Penzoldt as being directly responsible for the development of conditions favoring the development of tuberculosis. Jaeger, however, believes that, through strong pressure due to coughing, the expansion leads to trauma of the apices, the repeated trauma predisposing to the development of tuberculosis.

The question is raised: How can the decreased movement of the apex predispose to tuberculosis when therapeutically artificial pneumothorax produces beneficial results? Experimentally Shaw (17) has injected tubercle bacilli into normal rabbits with artificial pneumothorax and has observed a localization of the tuberculosis in the collapsed lung. Beitzke (14) explains this apparent contradiction on the basis of a difference in conditions. In the case of therapeutic artificial pneumothorax the lung is already infected and the collapse meets the fundamental surgical principle which requires rest to all infected parts. In the apex there is not a complete stoppage of respiratory movement as is usually obtained in artificial pneumothorax. Furthermore, in the lung collapsed by artificial pneumothorax there is a venous congestion and a stopping of the lymph circulation, whereas in the apex the lymph circulation is only retarded and there is a relative anaemia.

Orsos and Loeshcke (18) have performed experiments upon which they based the conclusion that the apices are especially well ventilated. However, these experimenters have considered the lung to be stretched during inspiration only in a craniocaudal direction by a force which attacks all caudal points with equal intensity and have failed to take into account many factors such as the arching of the diaphragm, the ribs and rib movements, the transverse tension, the bronchi and the varying elasticity of the lungs, which, according to Tendeloo (12), influ-

ence the respiratory volume changes in the various parts of the lung. Through a study of these various factors, Tendeloo reached the conclusion that during quiet respiration the paravertebral cranial lung parts show the least volume changes and therefore were least ventilated and have relatively less blood and lymph circulation. That the apical region is, during normal respiration, less well aerated than the remaining portions of the lungs thus seems to be a fairly well-established fact.

Many of the investigators have entirely disregarded the question of aeration of the lungs and have built up theories based on various observations.

Walsh (19) advanced two reasons for the frequency of apical tuberculosis, namely, the physical configuration of the bronchial tubes which allowed tubercle bacilli to reach the apices more readily than other parts of the lungs; and a greater mechanical activity of the apices as compared with the rest of the lung, a conclusion reached after reviewing evidence obtained by therapeutic, bacteriological, microscopic, macroscopic and physical methods.

In the assumption of the orthograde posture, the apical portions of the lungs become anaemic, and, according to Phillips (20), this produces conditions which afford opportunities for the lodgment and multiplication of tubercle bacilli. As further evidence of the importance of posture in the determination of the site of localization of tuberculosis, Phillips cites the frequency of tuberculosis in the caudad lobes of the lungs of the cow, a pronograde animal in which the caudad lobe is the highest part of the lung and corresponds in position to the apex of the human lung.

Reinders (21) believes that there is no predisposition of the apex for tuberculosis. He believes that tuberculosis occurs more frequently in the apex because the apex is more exposed to tuberculosis. He believes that the bacilli reach the apex from the cervical lymph nodes *via* adhesions between the lymph nodes and pleura.

Many of the earlier clinicians, such as Aufrecht, Gordeler, Grantz, and von Behring (22), believed that tubercle bacilli passed from the cervical lymph nodes to the bronchial lymph nodes and thence *via* the blood to the lungs. Others, such as Grober, Klebs and Beckman (22) believed that tubercle bacilli reached the supraclavicular lymph nodes from the pharynx and passed directly to the apices of the lungs. Grober (23) writes of an experiment in which he injected india-ink into the pharyngeal tissues of animals and found that the cervical lymphatics deposited them

on the apical pleura and then passed through to the parenchyma of the lungs. Zwaluwenberg and Grabfield (22) and more recently Grabfield and Miller (24) noted the great incidence of apical pleuritis, 93 per cent occurring in cases of tonsillar infection. They therefore suggested the following route of infection: tonsils or any other part of Waldeyer's ring, *via* the cervical lymphatics to the apical pleura and thence to the parenchyma of the lung apex.

Apical tuberculosis theoretically may be due to aerogenous, lymphatic or blood-stream infection. The possibility of aerogenous infection of the apices is however diminished by the fact that the apices are relatively less well ventilated than the remaining portions of the lungs and therefore fewer bacilli will be aspirated into the apices; aerogenous infection would therefore not explain the great frequency of apical tuberculosis. Inasmuch as the lymphatic drainage of the lung is toward the hilum except for the subpleural portions, there cannot be any lymphatic extension from a primary tuberculous focus or its concomitant hilar lymph-node tuberculosis to the apex. The lymphatic extension from a tuberculous focus in Waldeyer's ring as advanced by Zwaluwenberg and Grabfield, Miller, and others would not explain the great frequency of apical tuberculosis, since tuberculosis of Waldeyer's ring is much less frequent than apical tuberculosis. Blood-stream infection is therefore the only other possible explanation for the frequency of apical tuberculosis. That apical tuberculosis for the most part follows a blood-stream infection has for many years been maintained by Huebschmann (27) and others.

Parrot, Ghon, and others (25) have conclusively demonstrated that the site of primary tuberculous infection in an infant or child is in the lower half of the upper lobe or in the upper half of the lower lobe and only rarely in the apices. This site of implantation is marked by the formation of a primary tubercle with extension of the tuberculous process along the lymphatics to the regional lymph nodes at the hilum of the lung. This primary or Ghon complex may undergo either progressive or retrogressive changes or it may remain stationary. Retrogressive changes are the most common if the child survives the primary infection; the primary tubercle becomes encapsulated by dense hyalinized connective tissue which may undergo calcification, ossification or cicatrization. Tubercle bacilli may remain dormant within these latent and retrogressive lesions.

It is conceivable that a few bacilli may escape now and then into the

blood-stream, from which they may be recovered as acid-fast bacilli or perhaps as one of the various mutation forms which the tubercle bacillus has been observed to undergo. This escape of tubercle bacilli into the lymph- and blood-streams would be most marked when for any reason,—physiological, as occurring at the time of puberty, or otherwise,—the resistance of the individual is decreased; the primary complex, which had thus far remained stationary or had undergone regressive changes, will then undergo progressive changes, its capsule in this way becoming more permeable to the tubercle bacillus. That tubercle-bacillus bacillaemia actually exists has been shown experimentally by blood-culture; this is further substantiated by the clinical occurrence of extra-pulmonary tuberculosis in individuals with active or latent pulmonary tuberculosis. That tubercle bacilli occur more often in the blood-stream than experiments have led us to believe is maintained by Huebschmann (27), who explains the absence of a miliary tuberculosis in spite of the presence of tubercle bacilli in the blood-stream by the failure of the tubercle bacilli to multiply in the blood unless the protective forces of the body do not function. Tubercle bacilli thus enter the thoracic duct from the tuberculous complex in the lymph node and are carried then through the superior vena cava, the right heart and the pulmonary arteries back to the lungs where apical tuberculosis occurs. Why the tubercle bacilli brought to the lungs in this manner should localize in the apices has been difficult to explain. That deficient aeration of the apices as compared with the rest of the lung is the determining factor in predisposing to apical localization has been the predominant theory for many years, but the exact mechanism whereby it acts has not been established. One might explain apical localization in the following manner: If the tubercle bacilli carried to the lungs by the pulmonary arteries were excreted into the alveolar spaces, those bacilli excreted into the alveolar spaces of the apices where aeration is deficient will be able to gain a foothold and result in the development of apical tuberculosis, while those excreted into the alveolar spaces of parts of the lung other than the apices will not be able to develop because of the constant inspiration and expiration of air. This theory is based on the assumption that there is an excretion of tubercle bacilli into the alveolar spaces. That such an excretory process occurs has been advanced by Huebschmann (27) following a histological study of the miliary tubercles in miliary tuberculosis.

EXPERIMENT

In order to prove definitely the presence of such a process the following experiment was performed. In this experiment an attempt was made to approximate as closely as possible conditions existing in man by the use of monkeys as the subjects of the experiment. The experiment was carried out in the following manner:

Two and one-half cubic centimetres of a suspension of live human tubercle bacilli (containing 1.3 mgm. of a culture of tubercle bacilli per cubic centimetre) were injected into the saphenous veins of each of six monkeys. The monkeys were then bled to death at intervals of five minutes, fifteen minutes, one hour, six hours and twenty-four hours. The lungs were immediately fixed by the injection of 10 per cent formaldehyde by means of a syringe into both the pulmonary artery and the bronchi. Paraffin sections were made of each lobe of the lung, and were then stained with the ordinary haemalum-eosin stain and with the Ziehl-Neelsen carbol-fuchsin stain for tubercle bacilli. Similar studies were also made of other organs,—liver, spleen and kidneys.

Examination of the various sections revealed the following:

In the monkey killed five minutes after injection there were no apparent gross changes in the lungs. Ziehl-Neelsen staining revealed small groups of acid-fast rods and granules, tubercle bacilli, engulfed in endothelial cells and macrophages which were apparently free within the smaller capillaries (figure 1). A few polymorphonuclear cells and macrophages were occasionally found to be grouped about the macrophages containing tubercle bacilli. The localization of the tubercle bacilli did not bear any relation to the dense areas of peribronchial infiltration with pigment, polymorphonuclear cells and round cells, which were observed in all lung sections in each of the monkeys.[2] There did not appear to be any appreciable difference in the number and distribution of tubercle bacilli in the various lobes of the lung in this or any of the other monkeys.

A partially collapsed right upper lobe with a few pleural adhesions and a number of discrete gray nodules varying in size up to one centimetre in diameter were observed grossly in *the lungs of the monkey killed after fifteen minutes*. This doubtless is evidence of an old tuberculosis, but it did not affect the results of our experiments since the localization

[2] The monkeys used in this experiment had been previously used in experiments in which they were exposed to extremes of temperature; also, they had been injected repeatedly with varying doses of streptococci. This probably accounts for the various macroscopic changes as well as for the dense areas of peribronchial infiltration.

of tubercle bacilli in this pathological portion of the lung tissue was similar to that in the normal lung tissue. Microscopically these areas appeared as dense collections of round cells and polymorphonuclear cells with an occasional multinucleated giant cell and focal areas of dense hyalinized connective tissue. Carbol-fuchsin staining showed in the normal portions of the lungs clumps of tubercle bacilli ingested by endothelial cells and macrophages of the alveolar septa; some of these bacilli-containing cells were found in capillaries. An occasional focal collection of polymorphonuclear cells, monocytes and macrophages were noted about macrophages containing tubercle bacilli, but again there was no apparent relation to the larger dense areas noted above.

The lungs of the monkey killed after one hour were free from any macroscopic changes. Ziehl-Neelsen staining showed bacilli to be more numerous than in previous animals. Clumps of tubercle bacilli were noted in macrophages, about many of which were collections of macrophages and polymorphonuclear cells, and, in these areas, fixed endothelial cells appeared swollen and prominent, some containing tubercle bacilli. Capillaries were found in some areas to contain clumps of bacilli free in their lumina. In one area a vessel appeared to be widely dilated and within its lumen a clump of macrophages and polymorphonuclear cells were observed, the central cell of which contained ingested tubercle bacilli.

A firm nodule with a necrotic centre was observed in the right upper lobe of *the monkey killed three hours after injection.* In addition, section revealed focal areas of bronchopneumonia. Tubercle bacilli were found in moderate numbers in locations similar to that described in the previous animals except that the reaction about the bacilli was more marked. Here again the old pulmonary pathological process did not affect the purpose of this experiment, inasmuch as it had no effect on the localization of the tubercle bacilli.

The monkey killed after six hours showed no apparent macroscopic pulmonary changes, but microscopically some interesting observations were made. In addition to showing tubercle bacilli in locations as noted in the lungs of previous animals, bacilli were observed in (1) greatly dilated blood-vessels, (2) in macrophages attached to the surface of the alveolar septa, and (3) within macrophages which were free in the alveolar spaces. Single bacilli and clumps of bacilli were found in macrophages free in the lumina of widely dilated veins and surrounded by other macrophages, polymorphonuclear cells and red blood cells (figure 2); a few were noted

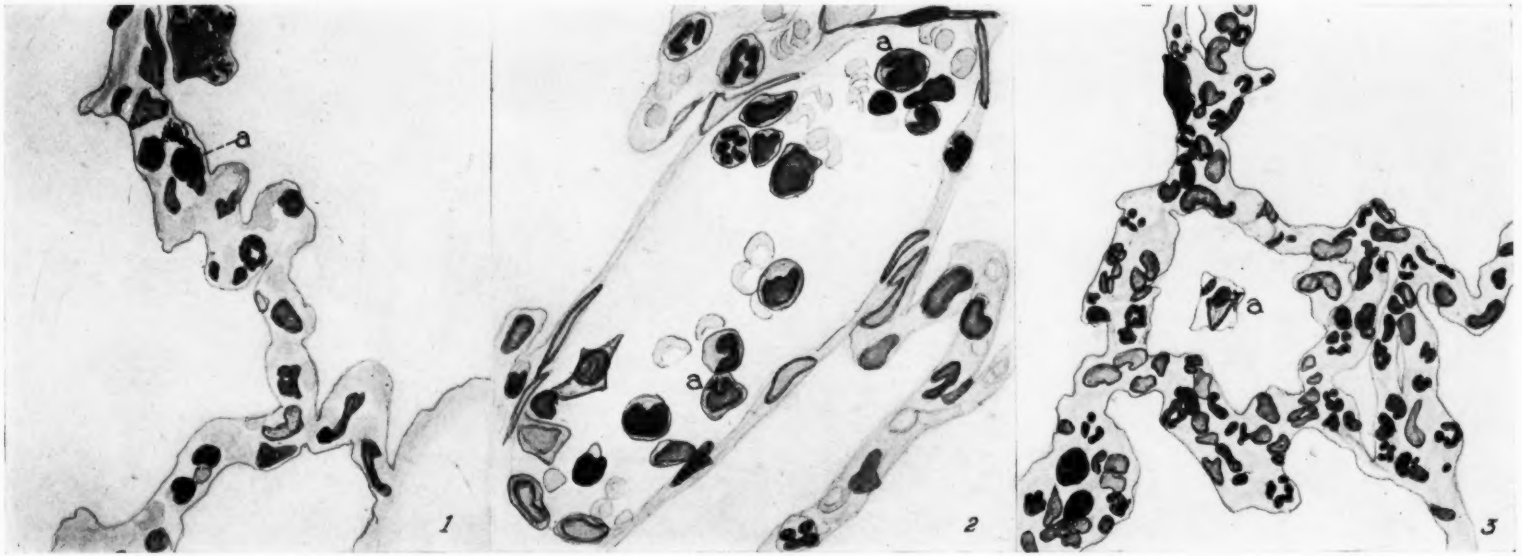

FIG. 1. Fixed endothelial cells (a) with ingested tubercle bacilli in the right upper lobes of the lung of a monkey killed five minutes after the intravenous injection of a suspension of tubercle bacilli.

FIG. 2. Macrophage (a) with ingested tubercle bacilli in the lumen of a dilated vein in the right upper lobe of the lung of a monkey killed six hours after injection.

FIG. 3. Macrophage (a) with ingested tubercle bacilli free in the alveolar space of the left lower lobe of the lung of a monkey killed six hours after injection.

in macrophages adherent to the walls of these vessels. Tubercle bacilli were further noted in macrophages which were in the process of being extruded into the alveolar spaces. Further, macrophages containing tubercle bacilli were found in a number of areas free within the alveolar spaces (figure 3); in one area, a macrophage containing tubercle bacilli and free in the alveolar space was surrounded by other macrophages and polymorphonuclear cells.

Similar findings were noted in *the lungs of the monkey killed twenty-four hours after inoculation*. In addition, there were extravasations of blood into the alveolar spaces.

Microscopic examination of the liver, spleen and kidneys revealed tubercle bacilli to have been ingested by the various reticuloendothelial elements as early as five minutes after injection.

SUMMARY AND CONCLUSION

It is thus apparent that following their intravenous injection many tubercle bacilli are picked up by the endothelial cells of the capillaries of the lungs. They are then ingested by macrophages and either enter the pulmonary veins to be distributed over the entire body or are excreted into the alveolar spaces. The gradual extrusion of macrophages containing tubercle bacilli into the alveolar spaces has been observed microscopically. Excretion of tubercle bacilli into the alveolar spaces is thus a proved fact.

In conclusion, apical tuberculosis may be due to an excretion into the alveolar spaces of the apices, where aeration is deficient, of tubercle bacilli from the blood-stream, the tubercle bacilli having reached the blood-stream from the primary tuberculous complex.

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ACUTE SUBAPICAL VERSUS INSIDIOUS APICAL TUBERCULOSIS

III. A Report of 1,000 Cases[1]

BRUCE H. DOUGLAS, JOHN P. NALBANT AND MAX PINNER

In two earlier communications from the William H. Maybury Sanatorium (1) (2) attention was drawn to the relationship between subapical and apical pulmonary tuberculosis as brought out in a study of 200 cases. Realizing at the time that this was too small a number to draw definite conclusions from, it was thought advisable to continue the study. The series has now been brought up to 1,000 cases, and it is the purpose of this paper to present and discuss the tabulation of this larger number in a further attempt to clarify the pathogenesis of pulmonary tuberculosis with special reference to what we have termed the *acute subapical lesion*, elsewhere referred to as the "Assmann focus," the "infraclavicular infiltrate" or the "early infiltrate."

It is not intended to add any additional classification to an already overclassified subject, but to present the evidence in hand as of extreme importance in assisting the clinician to make an accurate diagnosis that points out the location and quality of the lesion encountered and, having such a concept, further assists him to apply intelligently the proper treatment.

As indicated in the first communication on this subject, it is not within the scope of this study to attempt to show the mode of entrance of the tubercle bacillus into the body and the phenomena connected with first infection, but it is contended that clinical observations such as these can be helpful in giving a picture of the course of events in the development of many pulmonary lesions from the beginning of the actual clinical disease to its later stages. This course has been found to be acute in most of the typical subapically located (initial) lesions, a fact that differs very materially from the older views on the incipiency of pulmonary tuberculosis. Most of the older text-books have described the disease as beginning with a very small apical lesion which insidiously

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

spreads caudalward and which is so elusive from the standpoint of symptoms and physical findings that only the very keenest diagnostician could ever detect it. However, the deplorable situation still exists that the majority of patients present themselves first with far-advanced disease; and incipiency, as seen in the apical lesion, seldom is found; and from this study the lesion is believed to be rarely incipient but usually represents a long-standing low-grade process that is very often quite innocuous. The acute subapical lesion is the more frequent as the truly incipient lesion, and such lesions often develop into far-advanced disease before they are recognized, for the reason that they increase rapidly in extent, as will be shown later.

The data collected in this larger series were the same as previously compiled for the preliminary report, namely, a special study of each case was made stressing the following points:

1. History:
1. Date of onset
2. Duration from onset to first X-ray picture
3. Type of onset
4. Course since onset

2. X-ray interpretation:
1. Extent of involvement
2. Presence and localization of cavities
3. Apical involvement

Realizing that the history of the time and nature of the onset is of the greatest importance, we have carefully gone over these points with each individual patient and have been able in most instances to get a quite definite statement as to the beginning of the trouble.

The duration of the disease from the onset to the first X-ray film is used as a significant period, because it represents usually the period before an accurate diagnosis is made, and what has occurred in the progression of the lesion during this time indicates the acuteness of the process in large degree. The "type of onset" has to do with whether it has been sudden, insidious, or insidious, with later acute exacerbations.

Under the heading *X-ray interpretation* the extent of the lesion was determined according to the Diagnostic Standards of the National Tuberculosis Association. The presence or absence of cavities was recorded and their location as to whether apical or subapical. In determining the presence or absence of apical involvement three groups were

made, namely, "apices free," in which no involvement in the parenchyma of the apex could be found; "apices involved," in which the apical parenchyma was definitely involved; and "apices relatively free," in which cases it was quite evident that the main lesion was subapical but might extend slightly into the apical parenchyma, or in which the apical involvement was relatively slight as compared with the more extensive subapical lesion.

RESULTS

Table 1 presents the data on 1,000 cases which form the basis for the following analysis. The large percentage of sudden onsets is quite striking, and the small number who had both an insidious onset and, later, insidious course is at variance with the usual text-book picture of the onset and course of pulmonary tuberculosis.

TABLE 1

Crude data

	NUMBER OF PATIENTS	PERCENTAGE OF TOTAL
1. Onset and course:		
1. Sudden onset	544	54.4
2. Insidious course	215	21.5
3. Insidious onset: later acute exacerbations	241	24.1
Total	1,000	100.0
2. Extent of involvement:		
1. Minimal	165	16.5
2. Moderately advanced	330	33.0
3. Far advanced	505	50.5
Total	1,000	100.0
3. Apical involvement:		
1. Apices free	210	21.0
2. Apices involved	650	65.0
3. Apices relatively free	140	14.0
Total	1,000	100.0
4. Cavities:		
Present in apex	659	65.9

The numerous tables presented are arranged to show the relative importance of the acute onset and the subapical location of the lesion in many instances.

Table 2 indicates that free apices are present much more frequently in patients with sudden onset.

TABLE 2

Relation between apical involvement and course of disease

	APICES INVOLVED (650 PATIENTS)		APICES FREE (210 PATIENTS)		APICES RELATIVELY FREE (140 PATIENTS)	
	Number	Per cent	Number	Per cent	Number	Per cent
Sudden onset	270	41.6	167	80.0	107	77.0
Insidious course	173	26.4	27	12.9	15	10.0
Insidious onset: later, acute exacerbations	207	32.0	16	7.1	18	13.0

That apical involvement increases with the duration of the disease is clearly shown in table 3, column 1. Column 2 indicates the more marked increase in apical involvement in sudden-onset cases as compared with insidious-onset cases listed in column 3, which show from the onset a high percentage of apical involvement.

TABLE 3

Relation between apical involvement, duration of symptoms and course of disease

DURATION OF SYMPTOMS	ALL PATIENTS			PATIENTS WITH SUDDEN ONSET			PATIENTS WITH INSIDIOUS COURSE		
	Number of patients	Apices involved		Number of patients	Apices involved		Number of patients	Apices involved	
		Number	Per cent		Number	Per cent		Number	Per cent
6 months and less	338	162	48.0	241	88	36.5	72	49	68.0
More than 6 months to 2 years	394	262	66.5	209	115	55.0	86	74	86.0
More than 2 to 5 years	162	129	80.0	58	36	62.0	38	32	84.2
More than 5 years	106	97	91.5	36	31	86.1	19	18	94.7
Total	1,000	650	65.0	544	270	49.6	215	173	80.0

The inverse to table 3 is shown in table 4, in which it is shown that free apices grow rapidly less free with increased duration of the disease in patients with sudden onset.

TABLE 4

Relation of duration to the frequency of uninvolved apices in patients with sudden onset

DURATION OF SYMPTOMS	NUMBER OF PATIENTS	APICES FREE	
		Number	Per cent
6 months and less	240	112	46.6
More than 6 months to 2 years	210	64	30.4
More than 2 to 5 years	58	15	25.8
More than 5 years	36	3	8.3
Total	544	194	35.6

Table 5 shows that patients with free apices are, in average, diagnosed much earlier in the disease that those with involved apices, presumably because their faster development enforces earlier detection by patient and physician.

TABLE 5

Relation of apical involvement to average duration of symptoms and to course of disease

	APICES FREE		APICES INVOLVED	
	Number of patients	Average duration of symptoms in years	Number of patients	Average duration of symptoms in years
Sudden onset	167	0.9	270	1.9
Insidious course	27	1.13	173	2.0

The tendency for the patient with a sudden onset to develop cavitation early and frequently is shown in table 6, where it is seen that the percentage of cavities present in the "sudden onset" group is high and remains high regardless of duration; so that 71.1 per cent of this group had cavities in an average duration of 1.46 years, whereas the "insidious onset" group only had cavitation in 52.5 per cent with an average duration of 1.88 years, the cavities becoming more numerous with increased duration of disease in this latter group.

TABLE 6

Relation of course of disease to presence of cavities and duration of symptoms

DURATION OF SYMPTOMS	SUDDEN ONSET			INSIDIOUS COURSE		
	Number of patients	Cavities present		Number of patients	Cavities present	
		Number	Per cent		Number	Per cent
6 months and less	240	163	67.9	72	29	40.2
More than 6 months to 2 years	210	147	74.7	86	53	61.6
More than 2 to 5 years	58	40	68.9	38	20	52.6
More than 5 years	36	27	75.0	19	11	57.8
Total	544	387	71.1	215	113	52.5
Average duration of symptoms	1.46 years			1.88 years		

Table 7 presents the distribution of the cavity-bearers into the three clinical groups divided as to onset and course. It is most interesting to note that 60 per cent of the cavity-bearers fall into the sudden-onset group and that this percentage is even higher in the patients in whom the

disease has been present less than six months. The fact that this relation decreases markedly with increased duration in the sudden-onset group points to a high mortality in the first two years for these patients. The insidious-course group, on the other hand, represents only 17.2 per cent of the cavity-bearers; while in the third group there are relatively few cavity-bearers at six months, and the number increases after acute exacerbations have occurred, as indicated here.

TABLE 7

The distribution of 659 cavity-bearers according to clinical course of disease

DURATION OF SYMPTOMS	TOTAL NUMBER OF PATIENTS	SUDDEN ONSET		INSIDIOUS COURSE		INSIDIOUS ONSET WITH ACUTE EXACERBATIONS	
		Number	Percentage of total	Number	Percentage of total	Number	Percentage of total
6 months and less	211	163	77.2	30	14.2	18	8.5
More than 6 months to 2 years	278	165	59.3	53	19.0	60	21.5
More than 2 to 5 years	103	40	38.8	20	19.4	43	41.7
More than 5 years	67	28	41.7	11	16.4	28	41.7
Total	659	396	60.0	114	17.2	149	22.6

Table 8 demonstrates the striking difference in duration between the "apices involved" group and those with "apices free," which emphasizes the more rapid progression of the latter group. It indicates further the higher percentage incidence of cavities in the "apices free" group.

TABLE 8

Relation of course of disease to presence of cavities and apical involvement

	SUDDEN ONSET			INSIDIOUS COURSE			ALL PATIENTS WITH CLEAR APICES OR APICES INVOLVED			AVERAGE DURATION OF SYMPTOMS
	Number of patients	Cavities present		Number of patients	Cavities present		Number of patients	Cavities present		
		Number	Per cent		Number	Per cent		Number	Per cent	
Apices involved	270	211	78.1	175	88	50.2	650	436	67.1	2.09 yrs.
Apices free	167	96	57.4	27	7	25.9	210	109	51.9	0.65 yrs.

Taking the whole group regardless of type of onset, it is plainly evident, as shown in table 9, that the extent of the lesion is not dependent upon the duration of symptoms to any appreciable extent, as the percentage of far-advanced cases is high, regardless of duration, and is practically as

low in the five-year group as in the group of shorter duration, presumably due to the survival of patients whose lesions are not extensive.

TABLE 9

Relation of duration of symptoms to extent of lesion

DURATION OF SYMPTOMS	NUMBER OF PATIENTS	FAR ADVANCED	
		Number	Per cent
6 months and less	339	152	44.8
More than 6 months to 2 years	393	224	56.9
More than 2 to 5 years	161	80	49.6
More than 5 years	107	49	45.7
Total	1,000	505	50.5

In table 10 the far-advanced cases are divided into those with sudden onset and insidious course to show the relative duration; and again is pointed out the rapidity with which the sudden-onset cases progress, for the percentage of advanced cases is high and continues high regardless of duration of symptoms, while the percentage of far-advanced lesions does not change materially (and certainly not progressively) with the duration of the disease.

TABLE 10

Relation of duration of symptoms to extent of lesion and course of disease

DURATION OF SYMPTOMS	SUDDEN ONSET			INSIDIOUS COURSE		
	Number of patients	Far advanced		Number of patients	Far advanced	
		Number	Per cent		Number	Per cent
6 months and less	240	169	70.4	72	31	43.0
More than 6 months to 2 years	210	178	84.7	86	56	65.1
More than 2 to 5 years	58	43	74.1	38	22	57.8
More than 5 years	36	28	77.7	19	10	52.6
Total	544	418	76.8	215	119	55.8
Average duration of symptoms	1.46 years			2.16 years		

In this table all patients having cavities, regardless of the extent of the lesion, are added to the group of far-advanced lesions by extent only.

In table 11 it may be noted that patients with apical involvement usually have an insidious onset, whereas patients with free apices are most frequently found to have a sudden onset. This is largely a restatement of table 2.

TABLE 11

Relation between course of disease and apical involvement

	SUDDEN ONSET (544 PATIENTS)		INSIDIOUS COURSE (215 PATIENTS)		INSIDIOUS ONSET: LATER, ACUTE EXACERBATIONS (241 PATIENTS)	
	Number	Per cent	Number	Per cent	Number	Per cent
Apices involved	270	49.6	173	80.4	207	85.8
Apices free	167	30.7	27	12.5	14	5.8
Apices relatively free	107	19.6	15	6.9	20	8.2

TABLE 12

The distribution of 505 far-advanced lesions according to clinical course of disease

DURATION OF SYMPTOMS	NUMBER OF PATIENTS	SUDDEN ONSET		INSIDIOUS COURSE		INSIDIOUS ONSET: LATER, ACUTE EXACERBATIONS	
		Number	Per cent	Number	Per cent	Number	Per cent
6 months and less	152	121	79.6	20	13.1	11	7.2
More than 6 months to 2 years	224	141	62.9	40	17.8	43	19.1
More than 2 to 5 years	80	35	43.7	15	18.7	30	37.5
More than 5 years	49	24	46.9	6	12.2	19	38.9
Total	505	321	63.5	81	16.0	103	20.4

Table 13 needs no special discussion, as it clearly shows a marked difference in the clinical characteristics of the subapical lesion as against the apical lesion.

TABLE 13

Some significant data for cases of acute subapical and of insidious apical tuberculosis

	TOTAL NUMBER	SUDDEN ONSET AND APICES FREE		INSIDIOUS COURSE AND APICES INVOLVED	
		Number	Percentage of total	Number	Percentage of total
Far advanced within 6 months' duration	67	50	74.6	17	25.3
Far advanced within 1 year's duration	105	67	63.8	38	36.1
Far advanced, regardless of duration	174	99	51.4	76	43.4
Cavities present within 1 year's duration	110	77	70.0	53	48.1
Cavities present, regardless of duration	230	133	57.3	97	42.1
Average duration of symptoms		0.9 years		2.0 years	
Number of patients		167		173	

DISCUSSION

Realizing that statistical data based on small numbers is always open to question, it has been extremely interesting to note that with few exceptions the percentage distribution of the 1,000 cases varies only slightly from the percentage found in the first 200 cases studied. Some figures show significant changes, comparing our first publication in 1929 with the present study: the percentage of minimal cases has increased more than 50 per cent and the moderately advanced group shows an increase of about 20 per cent. The percentage of cavity-bearers, however, shows only a slight decrease. The encouraging trend shown in these figures is further emphasized by the fact that 33.8 per cent of patients in this report fall into the group of six-months-or-less duration; our first paper showed only 16.5 per cent belonging in this early group. This shift has materially altered all our data on duration of symptoms in relation to anatomical developments.

These changes are dependent on the promptness of the diagnostic work and on the readiness of the patient to seek medical care. Those data, however, that depend on the natural development of the disease are essentially similar now and in the material of 1928.

In the light of these more extensive data, it has not been necessary to alter the original conclusions at all. It is also a fair commentary of the reasonable accuracy of the method of study that four different workers have from time to time been engaged in this work over a period of four years and that the results of all these have corresponded very closely.

That the subapical lesion is of special clinical significance and develops with a more or less definite type of onset and rapidly progressive course, if untreated, has herewith additional support, for the conclusions drawn from the preliminary report may be re-stated with assurance of their truth as far as this method of study can establish it. These conclusions are:

1: Sudden onset is more frequent in pulmonary tuberculosis than is insidious onset (table 1).

2: Apical involvement is not a characteristic of incipiency but it occurs in the majority of cases after the incipient stage has passed (tables 3 and 4).

3: The extent of the lesion does not bear a direct relation to the duration of the disease. Of all patients reaching the far-advanced stage, the majority does so within the first half-year (tables 9, 10 and 12).

4: Cavitation is not a late occurrence; its frequency is nearly the same at any stage of the disease (tables 6 and 7).

5: Apical involvement bears a close relation to the type of the clinical course (tables 2 and 11).
6: An analysis of patients with pulmonary tuberculosis as to the two characteristics—"apices involved" and "type of onset"—leads to the differentiation of two different clinical types of disease (table 13).

Again it may be repeated that this is not to be construed as an attempt to classify pulmonary tuberculosis into confusing subgroups. On the other hand, a way of dealing with the disease by properly appreciating the history of onset and course, and the location and nature of the lesion, is herein pointed out as being extremely important in the matter of diagnosis, treatment and prognosis.

A patient with sudden onset has about one chance in one and a half to develop a cavity within the first six months, against a patient with insidious onset who has one chance in two and a half to do the same. Essentially the same figures are true for their relative chances to develop lesions far advanced in extent within six months.

The picture of the case with a typical subapical lesion, with its acute manifestations, as against the one with apical involvement, is as follows:

Onset:	*Type 1*	*Type 2*
1. Clinically	Sudden	Insidious
2. Anatomically	Acute bronchopneumonic infiltration	Discrete, productive tubercles
3. Localization	Subapical	Apical
Course:		
1. Clinically	In acute exacerbations	Slow progression or long period of standstill
2. Anatomically	Rapidly progressive or retrogressive changes interrupting chronic course	Very slow changes
3. Direction of progression	Toward apices and caudalward	Apicocaudal
4. Extent of lesion	Large extent already in "incipient stage"	Incipient stage identical with minimal stage
5. Cavitation	Early occurrence and frequent	Late occurrence and relatively infrequent
6. Duration	Relatively short	Very long
7. Healing	Absorption and /or massive fibrosis	Localized fibrotic scars

It is not our conclusion that the apical lesion is entirely benign but that it does take an entirely different course from the subapical lesion seems quite evident.

Fishberg and Shamaskin (3) have shown from a study of 1,000 cases the seriousness of the "subapical," or, as they termed it, the "infraclavicular" lesion as compared with the relatively benign apical lesion.

The subapical lesion, called by Redeker (4) the "infraclavicular infiltrate," is, as he points out, undoubtedly a reinfection phenomenon, whether it be the first reinfection focus or a "daughter infiltrate." The "daughter infiltrate" is definitely secondary to a demonstrable pulmonary lesion. It is true that the development of the subapical lesion represents the incipient stage of disease in more than half those persons who develop manifest clinical tuberculosis. In explanation of the development of many apical lesions it can be said that they are the result of healing of previous subapical lesions with migration or spread to the apex, and, with healing, the lesion becomes apical in location. Fischel (5) is quite correct when he points out that the recognition of apical tuberculosis is usually a late diagnosis and not a diagnosis of an incipient lesion.

Fischel's (5) attempt to correlate the concept of the "early infiltrate" with the Ranke scheme of classification is interesting but detracts, it would seem, from the immediate application of the concept to clinical use. It seems advisable at this stage in our knowledge to revise our teachings concerning the beginnings of clinical tuberculosis and recognize how helpful such an understanding can be not only in diagnosis, but also the great importance of the prompt application of proper treatment, because we are dealing with a disease which often has sudden onset and which is far more rapidly progressive than we have previously been wont to believe.

SUMMARY

1. Progressive and destructive pulmonary tuberculosis usually begins suddenly with exudative subapical lesions.

2. Lesions, far advanced as to extent, and excavations frequently develop within less than six months.

3. Processes leading to active progression and to excavation are most frequently associated with acute symptoms.

4. Physical signs and symptomatology (traditionally described as characteristic for "incipient pulmonary tuberculosis") are misleading for the detection of truly incipient subapical acute processes.

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THE STABILITY OF THE COLONY MORPHOLOGY AND PATHOGENICITY OF *BCG*[1, 2]

DOROTHY M. BEHNER

1. INTRODUCTION

It has been reported that virulent bacilli have been developed from *BCG* stock-strains by means of colony selection, cultivation on special media, and by reproduction within an animal host (Petroff, Branch and Steenken, 1929). In the paper here presented, report is made of work done with the object of developing a virulent substrain of *BCG*. Colony variation was closely watched as an indication of change in the character of the culture, but whether or not variation was accompanied by the acquisition of virulence was considered the most significant question to determine. It was considered essential to study variation in *BCG* in our laboratory because of at least four attitudes assumed toward immunization against tuberculosis. Workers who are convinced of its harmlessness advocate its use. Those who feel either that it is pathogenic for the rare individual with very low resistance, or that it is capable of responding to a changed environment and becoming gradually more virulent, or that it may produce a virulent "mutant," urge against its use.

Since regular animal-inoculation controls of the *BCG* vaccine preparation in the New York City Department of Health Research Laboratory were showing no capacity on the part of the vaccine for producing progressive tuberculosis in laboratory animals, it was thought advisable to try to induce dissociation by various means to see if a variant might be produced which had the attribute of virulence or to throw light on the possibility that the *BCG* might have lost that quality irreparably in its dissociation from a virulent culture. The preliminary steps were then to develop a substrain that would have a different colony morphology or growth characteristics so that it might be recognizably distinct from

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[2] Accepted by the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

the vaccine strain. Since virulence was to be the only acceptable criterion for significant dissociation, the sequel to all cultural manipulation was animal inoculation, with follow-up by subinoculation of animals with a culture recovered from the previous host. There is no serological method for discriminating small increments in heterogeneity among the acid-fast bacteria, the only laboratory methods being the detection of differences in species pathogenicity, or colony morphology, or growth characteristics.

Other strains of *Mycobacterium tuberculosis* were chosen for comparison with the *BCG* under similar laboratory procedure. These were avian rough and smooth strains and the Sasano-Medlar strain, considered to be a virulent bovine type.

2. EXPERIMENTAL

The four principal methods used to develop substrains: colony selection, cultivation on immune serum, cultivation on normal serum, and passage through animals, have been used by others. Antisera used were produced in rabbits by the usual methods; live inocula were used in *BCG* antiserum production, but the suspensions of the bovine type and avian strains were heated to 58°C. for ten minutes before inoculating them into rabbits. The antisera were used in media for the culture of their homologous type. Normal human serum was used in media on which *BCG* was planted. Sera were collected aseptically and used without preservative to the concentration of 10 per cent in Sauton's liquid medium adjusted to approximately pH 7.0 with dipotassium phosphate.

The controlling principle of colony selection was the seeding of suspensions made from an atypical, flat, nonpigmented, or more easily emulsifiable colony appearing on solid medium, on to plates of Petroff's gentian-violet-meat-egg, Loewenstein's congo-red-starch-asparagin-egg, and on unadjusted Bordet-Gengou potato-extract-agar-blood media using the technique developed at Trudeau laboratory for making the suspension, filtering it, and seeding it on plates and flasks.

Animals were inoculated by various routes with suspensions of bacilli, made by shaking with glass beads a known moist weight of bacilli and suspending them in saline solution. The material selected from solid media was never mass-growth. That from liquid media was usually mass-growth. Smears were made routinely from each animal at autopsy, from the site of inoculation if the subcutaneous route had been used, from the liver, spleen, lung, kidney, enlarged lymph nodes, and

occasionally from the testis, submaxillary lymph nodes and bone-marrow. Smears were stained with Ziehl-Neelsen carbol-fuchsin with heat, decolorized with acid-alcohol, and counterstained with methylene-blue for the most part. Digestions of abscesses, inguinal lymph nodes, liver, spleen and lung were commonly made with 3 per cent NaOH, neutralized with HCl to litmus, and planted upon several tubes of one or more of the solid media listed above. Growth on tubes planted with digested tissues were termed recovered cultures.

A. Colony Variation in BCG

Dissociation has been reported in the first seedings of *BCG* on egg medium (Petroff, 1927c). Petroff's gentian-violet-egg plates seeded with *BCG* may show the development of eight easily recognizable colony types, which, with their approximate percentage occurrence in 217 colonies of one plant on egg-medium plates seeded with a bile-potato grown culture, may be described as: high coiled throughout, 24 per cent (figure 9); high coil with beaded appearance on margin, 1 per cent; medium high coiled, 14 per cent (figure 15); horizontally arranged low coiled throughout, 19 per cent; low coiled with beaded margin, 18 per cent; beaded colony with fine cross furrows in coils which give beaded surface appearance, 21 per cent (figure 12 lower); single coil "crater" colonies, 2 per cent (much like those in figure 16); beaded surface colonies with irregular margins, 1 per cent. The "crater" form, regularly considered most typical, occurs much more frequently on egg medium in subsequent plants. The beaded surface forms, when planted, often yield exclusively coiled types on subplants. On Bordet-Gengou medium the forms listed appear together with others, that is, a high pile of growth with fairly smooth pedicles, making an irregular margin and a coiled or piled growth with flattened, spreading margin, usually wrinkled radially. Occasionally modified coil colony types appear on any medium; for example, figure 6 and figure 18 not precisely described in the above list but obviously coiled.

Later generations of plates seeded from colonies chosen for their tendency to be flat or spreading have shown extremely flat colonies. One strain produced colonies with tiny button centres and an almost transparent margin, less regular in margin than that produced by a virulent bovine strain used by us, but reproducing its own type with great consistency (figure 22). Another strain produced flat colonies with extremely delicate margins but with less consistency (figure 23).

A less fixed type is a small moist pile, with a smooth surface, and low and uneven in contour. It never reproduces its kind wholly, and a smear from such a colony shows a variety in bacillary morphological types.

Variations in colony morphology occur in any acid-fast strain, but the type to which a strain belongs can usually be read from the colony or from its progeny after re-seeding.

B. Animal Inoculations with Colony Forms Produced by Selective Fishing

From a substrain started from a vaccine culture of *BCG* came one of the most consistently flat-colony-producing strains, developed by fishing flat, beaded surfaced or spreading edges of colonies in successive generations for over a year. But in every generation typical *BCG* coil colonies as well as the flat colonies appeared. When a consistent production of colonies with small button centre, flat contour, slightly irregular margin, fairly delicate and transparent at the edge, and non-pigmented (figure 22), was obtained after 10 successive fishings of this type, the artificially propagated culture was lost. It lost its vitality very quickly, and seedings produced very few colonies and then none even on attempts at rapid successive seedings.

Of 6 animals inoculated with from 10 to 50 mgm. of the small flat colonies of the 9th generation from Petroff plates, and not from mass-culture grown from these colonies, a flat-colony-culture was recovered from one, dead 32 days later, and, from a second animal, a contaminated sparse growth. The recovery of a colony type not coarsely coiled was a rare phenomenon; the recovery of a type similar to that injected was unique in our experience. Bacilli were recovered only from the site of inoculation in both cases although the organs too were digested with sodium hydroxide, neutralized and seeded on Loewenstein and Bordet-Gengou media. None of the six showed macroscopic lesions. One was killed after 96 days and one died after receiving a subcutaneous inoculation of 0.5 cc. O.T., although no macroscopic lesions were present. Bacilli did not grow in digestion cultures of the organs of these.

Subinoculation of the flat, recovered culture, intracardially in the amount of 15 mgm., into 3 guinea pigs was successful in so far as the culture was again recovered from one after 70 days, and subinoculations into 5 guinea pigs of the third-passage series in amounts of 2 and 5 mgm. by the intracardial route has yielded 2 recovered cultures, which were used to inoculate 7 animals in the fourth-passage series with varying

amounts of culture by the route used in the earlier series. These animals were killed weeks later but cultures were not recoverable.

Other colony types were investigated. One smooth hemispherical colony on a Petroff plate was seeded; it yielded a growth with a finely beaded surface composed of long even-staining bacilli. Two rabbits received 25 mgm. each, and were killed after 138 and 159 days respectively. Six cultures of the tissues, including one abscess, failed to give growth. A guinea pig was inoculated with 10 mgm. It died in 13 days. The culture was recovered and subinoculated, but attempts to recover it from the second-passage series failed.

One substrain in this study, derived from a strain of the Calmette culture carried for some years on egg medium, was fished in successive generations for the veil-like edge and the margins approaching transparency. The plates developed 2 distinct classes of colonies, a coil colony (figure 19) and a most transparent colony (figure 23) with a delicate granular surface and so little raised in the centre that only a tiny button appeared there. None of the 10 animals inoculated with growth from the latter type of colony showed lesions other than microscopical or enlarged inguinal lymph nodes, and from only one that lived a short time was a culture recovered. The rabbits received as much as 50 mgm. The guinea pigs received 15 mgm. Most of the animals lived from 2 to 4 months, while one guinea pig lived 8 months.

Many animals, 20 guinea pigs and 13 rabbits, received small amounts of flattened horizontal coil colonies in the early days of the study. There was one culture, recovered from one guinea pig that lived 51 days after inoculation. Subinoculations were made into 2 guinea pigs, and in one a tumor at the site of inoculation was still observable 266 days later, but cultures of the lesion, inguinal nodes and spleen failed to yield growth.

There may be a colony difference developed which is sufficiently marked to distinguish varieties which might be named *rough* and *smooth*; but we find, as others do, that these varieties show no measurable difference in virulence (Tzeknovitzer, 1930; Reed and Rice, 1931; Birkhaug, 1933). The colony differences may have been exaggerated, too, since we find successive platings tend to show the typical coil colonies of *BCG* reappearing. If only one colony be planted in mass-culture preparatory to animal inoculation, the animal probably receives a preponderance of the coil-bearing types.

Another characteristic whose correlation to virulence is frequently stressed is ease of emulsification in saline solution. These flattest

transparent *BCG* colonies were less easily emulsified than growth from a virulent bovine type or than avian smooth colonies, but much more easily emulsified than coarsely coiled *BCG* colonies. We have shown that no virulence accrued to our cultures though others report a distinguishable difference with less morphologically distinct types (Begbie, 1931).

C. Deep Culture and Animal-Inoculation Experiments with Growth Obtained

By propagating *BCG* below the surface in an infusion bouillon enriched with Witte's peptone and then inoculating animals with the growth obtained after the second and the fourth generations, Dreyer and Vollum showed a startlingly uniform series of tuberculous guinea pigs with one strain, and another strain produced tuberculosis in a high percentage (Dreyer and Vollum, 1931, a). Saenz (1931) was unable to confirm their results, and reported that after some generations the culture lost its vitality as well. Kirchner (1931) reported that the pleomorphism obtained in deep culture, and on growth in antisera as well, reverted to the typical form on transplanting.

Initial generations in deep bouillon in this project were seeded with a culture from the substrain that had had a history of a flat colony on egg and two generations on liquid media, one of which contained human serum, and a culture from another substrain that had had a history of a flattened colony and one generation on liquid medium containing 10 per cent human serum. After the second generation in deep culture, plates of the second strain developed coil-type colonies only. Plates seeded with the first generation in deep culture of the first strain showed flattened-coil, high-coil and humped colonies. A flat colony seeded on plates a second time produced 120 colonies of broken-coil or crater-coil types, six of which showed secondary spreading growth and two had raised centres and flat margins. One of these latter was fished for a third generation on solid media and all the colonies produced were small with broken-coil surfaces, but the margins were neither flat nor spreading.

The animals inoculated with deep broth cultures form a small series because growth was limited.

Two guinea pigs and one rabbit received subcutaneously 7, 10, and 80 mgm., respectively, of the first substrain from the first generation in deep culture. One guinea pig showed an abscess at the site of inoculation

after 31 days. No growth was recovered from any of these animals, although they lived only 31, 30 and 42 days, respectively.

A guinea pig and a rabbit received subcutaneously 9 and 25 mgm., respectively, of the second strain from the second generation in deep culture. The rabbit was killed after 117 days, and showed on autopsy a lesion at the site of inoculation. From a digestion of the lesion a sparse growth, detectable by smear from the culture-tube, was recovered. Culture of the digested spleen remained sterile.

From the spleen of the guinea pig, dead after 57 days, a culture was recovered and used for subinoculating 3 guinea pigs. The recovered culture showed a coarse coil in basically crateriform arrangement with extensions on the border of the coil (figure 14). Twelve and a half milligrams moist weight was injected subcutaneously into two and the guinea pigs were killed after 83 and 88 days. One had shown a steady increase in weight, and at autopsy no lesions were apparent. The other showed a lesion at the site of inoculation only. Culture of the lesion failed to yield bacilli. The third guinea pig received 2 mgm. of the culture intracardially, was killed 121 days later, and showed no gross lesions except a pericardial abscess, presumably at the point of inoculation. A culture was recovered, however, from the splenic tissue after some weeks and used for inoculating 4 guinea pigs each with 2 mgm. intracardially. Two died after 54 and 74 days, respectively, and attempts to culture all organs failed to yield the strain. Two have lived nearly six months.

No measurable increment in the ability to produce lesions in guinea pigs has been observable in this strain although both cultivation in partial anaerobiosis and animal passage mark its history.

In other work reported from Dr. Park's Research Laboratory, a more extended series of animals received inocula from deep cultures of *BCG* without developing progressive tuberculosis, and plates seeded from the same cultures yielded colonies of typical *BCG* morphology (Mishulow, Park and Melman, 1932). Though confirmatory, the work quoted and that reported in the present paper were done independently.

D. Cultivation on Liquid Media Containing Serum; Colony Observations and Animal-Inoculation Experiments with the Growth Obtained

Cultivation of *BCG* on Sauton's medium containing human serum was confined largely to one strain selected by fishing for flat colonies on egg-containing media for one year, and kept on liquid media for 16 months during which time subinoculations into animals were made. The

colonies produced at the end of 16 months were flattened, and had granular or beaded surfaces and irregular margins. Colonies seeded after 6, 8 and 12 generations on this medium containing human serum are shown in figures 10, 11 and 15, respectively. However the colonies in figures 10 and 11 were not directly from the liquid parent culture, but had undergone 3 and 4 seedings respectively on solid media in an attempt to isolate a smooth-appearing type. The degree of failure is apparent. We have records of 61 animals inoculated with subcultures of the growth on liquid medium. Some received material from the third serum generation, and some from each generation thereafter through the ninth. Seven animals received material from the ninth generation and seven from the twentieth generation on liquid medium containing 10 per cent normal serum.

Summarizing briefly, it may be said that none of the animals showed gross tuberculous lesions other than abscesses at the site of inoculation when this was subcutaneous, and that not regularly.

In this group many of the large doses were given, such as 50, 80 and 100 mgm. Also, some of the longest lives were exhibited in this group. Seven animals were allowed to live longer than 230 days, 10 others longer than 180 days, and 7 longer than 140 days. Cultures were recovered from 12 of the 61 from 10 to 181 days after inoculation. Five cultures, recovered after 97, 105, 124, 149 and 181 days, respectively, represent some of the longest periods that the bacilli showed reproduction after being within the animal body; but two, the 124- and 181-day lives, gave such sparse growth that it was not macroscopic, and they were obtained from culture of the abscess after a subcutaneous inoculation of 80 mgm. One recovered strain went through five series of passage-animals before the strain was no longer recoverable. Another passage-experiment was attempted, but the majority died in second passage. For example, an animal receiving a culture grown for four generations on liquid medium died after 36 days. The recovered culture (figure 12) was subinoculated into 4 rabbits, 3 receiving 20 mgm. From none of these second-passage animals was a culture recovered.

The following story gives an example of the sequence of events and the false clues occurring in the course of this work:

Subsurface growth from serum-containing medium was seeded on plates. On the outer portions of two plates appeared hemispherical white, smooth-surfaced colonies, containing bacilli carrying one large acid-fast granule. Each colony was made the progenitor of a carefully

seeded subplant, and on one set of plates more of the very S-appearing colonies developed. Other colonies were crateriform, beaded or plateau-coil types, and contained many morphological types microscopically. The hemispherical colonies were collected for animal inoculation; 10 mgm. was injected subcutaneously into a guinea pig and 25 mgm. into a rabbit. The guinea pig died 13 days later and the strain was recovered from the site of inoculation. The rabbit lived 138 days and no culture could be obtained from digestion of its tissues. Two guinea pigs were inoculated with the material from the guinea pig's infected inguinal lymph node, and one received 5 mgm. of the recovered culture. The culture was not regained when the sites of inoculation from these three guinea pigs were subsequently digested and planted.

Normal serum produced no remarkable results, and in comparable cases it was not different in its action from immune serum.

Immune sera, some of which appeared to be able to agglutinate suspensions of homologous organisms in 1–1000 dilution, were added to make a 10 per cent solution in Sauton's synthetic liquid medium brought to approximately pH 7.0 with dipotassium phosphate. This buffer may have been too efficient to allow ready dissociation, since high alkalinity has been reported as inducing an R to S change (Reed and Rice, 1931 (a)) and the use of Na_2CO_3 resulted in a high alkalinity after a short incubation period. However when Na_2CO_3 was used in a series of cultures, repeating Sasano and Medlar's technique (Mishulow, Park and Melman, 1932), no increased pathogenicity was observed.

A certain proportion of colonies, developing on plates seeded with growth from media containing anti-*BCG* sera, even after the second generation showed horizontally arranged, cross-furrowed coil colonies, and wrinkled colonies with uneven margins, but coil and "crater" colonies also appeared even after 13 generations on liquid medium, eight of which contained immune serum. Figures 8, 9, 16 and 17 show the colony type produced on seeding on solid medium from cultures on antiserum. Figures 9 and 7 were seeded after the fifth subculture on immune sera.

A great deal of the cultivation on a liquid medium utilized a strain originally *BCG* but chosen from a certain colony on a plate of Petroff medium planted in April, 1930. The colony was flattened but coarse, and was considered to have dissociated toward the smooth type. Another substrain related to the above mentioned one was denominated "smooth" at the Trudeau Laboratory. For five generations over

eleven months these strains were selected by flat-colony fishings on egg plates, as were two other strains also cultivated to some extent on immune-serum-containing medium, one of which was the vaccine strain mentioned as eventually producing extremely flat colonies. A chronological chart (not presented herewith) of the work done shows many animals inoculated with various culture preparations: 14 lived longer than 3 months after inoculation, and 8 were killed after 82 days. None showed more than an abscess at the site of inoculation. Attempts were made to recover cultures from all the animals used; these were successful only twice from animals that had lived less than 3 months, and not from the 22 just mentioned.

E. Confusion Incident upon Infection with an Avian Strain

During this study a series of events occurred which were subject to misinterpretation. An egg culture of the Calmette strain was seeded on plates of Petroff's medium in December, 1930, for the purpose of obtaining discrete and perhaps atypical colonies. Individual colonies chosen for flatness and delicacy of marginal growth were so plated seven successive times, and then transplanted on to liquid Sauton's medium four times. At that time the culture was divided into 2 strains, one cultivated on Sauton's medium containing human serum and one on media containing anti-*BCG* serum. Pellicles developed with both coil formations and thin sheets, as is usual on liquid medium. Smears from both strains at this time showed long even-staining acid-fast bacilli with no granules. Both were considered pure cultures of *BCG* origin.

Animals were inoculated with a thirteen-day-old culture of an anti-*BCG* serum subculture in April, 1933, and plates were seeded from the same culture. The plates of Bordet-Gengou medium showed a majority of high-pile fairly coarsely coiled colonies, two small round moist, unpigmented colonies, and 15 flattened, irregular-edged colonies. Smears from the flattened colonies showed both short and long, tenuous acid-fast forms. The variation on the plates was not unexpected, and the idea of contamination of cultures did not occur to us at that time.

The animal results and subsequent cultures gave strong support to the idea that these were mixed cultures. Fifty animals were eventually used in studying this strain. Of eleven simultaneously inoculated in April with large doses (15 mgm. in the guinea pigs and 30 to 60 mgm. in the rabbits) of the material on the anti-*BCG* serum medium, then

unplated, so that at that time colony morphology was not known, five guinea pigs and four rabbits lived to be killed in August and showed no gross pathological changes except abscesses at the site of inoculation where this had been subcutaneous, with the exception of one guinea pig that showed gray areas in the lung. Upon digestion of the tissues, the culture was recovered from all abscesses and from the spleen or lung of intravenously inoculated rabbits and from the spleen, lung and abscess in the one guinea pig mentioned. One guinea pig died at the end of 51 days and no culture was recovered. The two rabbits died shortly; and from one which had lived 32 days two types of colonies appeared in the original digest on cultures, some broken-coil and some spreading with granular centres and thinner margins. The latter were thought to resemble a virulent colony type and showed very short bacilli in smears. It was subinoculated intravenously into 4 rabbits, subcutaneously into one guinea pig and intracardially into one guinea pig. The rabbits died within 25 days and showed extensive tuberculous changes; the guinea pigs showed no gross lesions; but cultures were recovered from the guinea pig inoculated intracardially and from all of the rabbits. The other guinea pig was killed after 112 days. Here obviously was a virulent culture with some differential effect on rabbits and guinea pigs.

Subinoculations of animals with cultures recovered from those of the original group that had been killed after 112 days and that had shown no gross lesions other than the abscess at the site of inoculation gave different pathological pictures in guinea pigs and rabbits, probably due to the fact that the intraperitoneal route was used. There were discrete large spherical abscesses on the mesenteries and viscera with some instances of lung invasion.

A control series of animal inoculations was carried out to test virulence, using 0.01, 0.1 and 10 mgm., respectively, of pooled cultures recovered from those of the original group that lived to be killed, and pooled cultures from two short-lived rabbits in the second-passage group subinoculated from the original rabbit that had died in 32 days. The smallest dose was regularly seen to have produced miliary lesions in the rabbits all killed from 50 to 65 days later, but to have produced generally less extensive disease in guinea pigs, possibly due to the different routes of inoculation. The intravenous route was used for rabbits and the intraperitoneal for the guinea pigs. One pooled culture was inoculated intravenously into hens. One hen that received 0.01 mgm. was living

81 days later, but the one that received 0.1 mgm. died in 30 days with extensive involvement of liver and spleen. Both avian smooth and rough types of colonies were recovered from the chicken.

Half of the rabbits that received larger doses died within a month; all showed gross tuberculous lesions in spleen and lung and in some the kidneys were involved. The culture was abundantly recovered from the spleen in all cases. The guinea pigs in the group showed pulmonary lesions with one exception.

Recovered cultures plated on Bordet-Gengou and Loewenstein media in the meantime showed a yellow pigment and a lack of coil-formation that stamped them as of avian variety and not *BCG*. We believe the culture was mixed before the time the first series of animals were subinoculated, that the avian components became more virulent with animal passage, that the strain was more than ordinarily virulent for guinea pigs after animal passage, and that the pathological picture was neither of the Yersin type of disease nor wholly of the avian R type described by Petroff (Winn and Petroff, 1933). The colonies were apparently of the R type and consistent in form except when recovered from the hen. Microscopically the organisms were extremely short, although occasionally long tenuous ones were seen; such have been seen in pure line cultures of avian R. The avian strain has been repeatedly shown to be far more labile from a dissociation standpoint than any mammalian strain. It has been reported to have changed in the animal body (Doan, 1930), though in our experience in both this group just discussed and in 24 animals receiving known dissociants of R and S types of avian tubercle bacilli, the colony type of the cultures inoculated and the colony type of the colony recovered were similar. That the virulence of avian tubercle bacilli may increase with animal passage has been made patent to us in three groups of animal experiments.

F. Recovered Cultures and Subsequent Animal-Passage Experiments

Tissues and/or lesions from 89.4 per cent of all *BCG*-inoculated animals were digested with 3 per cent NaOH, neutralized and planted on Loewenstein, Bordet-Gengou or Petroff medium, or on more than one kind. Cultures were recovered from only 33 (17.2 per cent); the culture-tubes of 137 (71.2 per cent) remained sterile for many months. The spleen, inguinal lymph nodes, and abscesses at the site of inoculation were most productive of viable organisms. Abscesses at the site of inoculation were present in 38 animals from which no culture could be obtained though

the lesion was undoubtedly formed in response to the inoculation. Smears were made from the tissues and lesions of all the animals cultured, but the distribution of positive and negative smears was not coincidental with success and failure in attempts to culture. From those animals from which cultures were recovered, positive smears were found in only 54.5 per cent, and in exactly half of these the positive smears were only from the abscess at the site of inoculation. In the other group from which cultures were not recovered, some positive tissue smears were obtained from 30 animals (21.9 per cent). Presumably these organisms represented a nonviable population; indeed 8 of the 33 recovered cultures were so feeble in their ability to grow that macroscopic growth was not obtained, and the transplants died out.

Recovered strains were used for animal-passage experiments. Some pertinent points of their histories may be noted. While 11 cultures may be said to have been in the animal body two weeks or less and 16 substrains in that environment less than a month, 11 inocula retained viability longer than two months, 7 were recovered after 100 days, 4 after 140, and 1, from a testicular inoculation, after 201 days in the animal body. The recoverability did not depend greatly on the amount inoculated either, the range in doses being from 2 to 112 mgm. moist weight. All routes of administration were utilized also.

Considering all the animals used, from 71 per cent of which no cultures were obtained, 20, or 10.3 per cent, lived two weeks or less after inoculation; 39, or 20.2 per cent, were in the group that died or were killed between 80 and 100 days after; 26, or 13.5 per cent, died or were killed between 101 and 126 days after, the latter two groups being the largest numerically for length of life after inoculation. The correlation between length of life after inoculation and recoverability of strain is shown by the fact that from 51 per cent of animals dying the first month cultures were obtained by tissue digestion, but cultures were recovered from only 10 per cent of those dying in the next four months. The dosage and route of inoculation also had a similar range for the two groups separated on a basis of culture recovery. Hence it seemed as though it might be possible to show an increase in virulence by an increased ability to live in the animal body.

Direct-passage experiments, using the site of inoculation for subinoculation, never went beyond the fourth passage, as contemporaneous culture controls showed no growth after that time, so that method was abandoned in favor of alternate animal inoculation and artificial labora-

tory culture, in order to know approximately how large a dose of bacilli was being injected into each animal.

A strain recovered from the spleen of a guinea pig that had received 9 mgm. subcutaneously and that lived 57 days after inoculation was passed through animals again, and recovered after 121 days' sojourn in the animal body from a guinea pig that had received only 2 mgm. intracardially. Of 4 guinea pigs of the third-passage series, two died in 54 and 74 days, respectively, showing no gross lesions, and digestion cultures of their tissues did not show growth, and two were killed after 5 months. No cultures were recovered. Another strain lost its viability, as far as attempts to culture it showed, in the whole group of third-passage animals. The total residence in animal tissues for the first two passages was only 37 days. Another strain survived two residences in the guinea pig, totalling 102 days, and from the third-passage series was recoverable after 13 days and not recoverable after 84 days. In another instance a strain survived 4 residences, totalling 152 days, in the animal body and was lost in the fifth-passage series. Thirteen passage strains were lost in the second-passage series.

G. Attenuation of a Virulent Bovine Strain

Dissociation of a moderately virulent bovine strain, B1, was reported by Petroff (1927, b). The appearance of colonies of the virulent bovine strain (Sasano-Medlar strain) used in the project here reported is not similar to that of either the "S" or "R" forms of B1 shown in Petroff's illustrations (1930). The Sasano-Medlar strain produces a tissue-thin film on liquid media, which is an "S" type growth (Reed and Rice, 1931, b); it grows with difficulty on glycerine-bile-potato medium, but profusely on glycerine-egg media such as Petroff's or Loewenstein's. The colony on solid media is greatly flattened, with a finely granular surface and slightly raised central growth which shows pigment at the centre upon aging. The most characteristic feature is a regularly extending circular transparent margin, much more delicate than any produced by *BCG* colonies.

The colony form of the most manipulated culture is very much the same as that of the stock culture on egg. The most that was accomplished was to develop a colony more raised in the centre, more coarsely granular on the surface, and bearing an irregular edge, and with a greater tendency toward pigmentation.

Cultivation on liquid media, plain or containing 10 per cent antiserum, did not change the character of the pellicle.

Examination of animal protocols shows that some, though variable, attenuation was produced in some by cultivation on glycerinated bile: 0.01 mgm. killed a rabbit in 40 days in 1931; 0.01 mgm. killed a rabbit in 64 days in 1932; 0.1 mgm. killed a rabbit in 19 days and 4 guinea pigs at the maximum of 35 days in the same year. Cultures with a checkered history of cultivation on glycerinated bile and egg were inoculated into rabbits and guinea pigs. One guinea pig receiving 0.3 mgm. was killed after 148 days and showed no gross lesions, but the culture was recovered. Another killed after 346 days showed no gross lesions. A rabbit receiving 0.1 mgm. lived 60 days and one receiving 0.01 mgm. was killed after 278 days and showed no lesions. The culture was not recovered. A larger number of animals showed only a difference in the time elapsing between inoculation and death of the animal. The end-result was then the same,—extensive organic lesions and generalized disease.

There seemed to be an indication that an attenuated strain might be produced, but the colony variants were not markedly distinctive, but more like those reported by others (Petroff, 1927; Reed and Rice, 1931, b).

H. Dissociation of Avian Strains

Many workers have found the Mycobacterium of avian tuberculosis susceptible of dissociation (Petroff, 1927, a; 1930; Winn and Petroff, 1933; Alexander, 1931; Doan, 1930; Kahn and Schwarzkopf, 1931 and 1933; Reed and Rice, 1931, b; Mishulow, personal communication to the author).

Two cultures of avian tubercle bacilli were generously given by Dr. M. C. Kahn, who stated that these were cultures of stabilized rough and smooth variants, respectively, derived from selected, single-cell cultures. Dissociation of these substrains from rough to smooth, and reversely, was undertaken and readily accomplished. This work is incorporated in the present report to show certain differences between dissociation of *BCG* and Sasano-Medlar strains, on the one hand, and avian strains on the other.

Miss Alexander used anti-sera; Dr. Kahn used normal serum, aging of the culture, animal inoculation and rapid transfer on Proskauer and Beck's solution A.

The media employed by us were Proskauer and Beck's solution A, Sauton's synthetic liquid medium, glycerine-bouillon, all with and without serum; and the solid media, Loewenstein's, Petroff's and unadjusted Bordet-Gengou.

Avian S on liquid media develops a tissue-thin surface film and a cloudy subsurface growth. Avian R on liquid media grows luxuriantly, producing a wrinkled pellicle, whose color deepens with age, and no subsurface cloud. On solid media, the Avian S colonies are typically smooth, moist, white and hemispherical. Avian R colonies on solid media are typically raised, with spreading edge and finely granular surfaces, white when young and becoming progressively chromogenic with age.

An Avian R culture plated after 3 generations on liquid media, two containing normal rabbit serum, developed among the R type 15 typical smooth colonies. Smooth colonies from plates seeded with Avian R culture that had passed 4 generations on liquid medium, one with serum and three without, when replated, yielded smooth colonies. Plates from a glycerine-bouillon-serum culture also yielded smooth colonies that, on replating, produced only smooth colonies. Figure 5 shows an S colony on a plate seeded from the 6th subculture of an originally R strain on liquid medium, two on medium containing normal rabbit serum, three on Proskauer and Beck's solution A.

Liquid-medium cultures planted with Avian R also developed in varying generations cloudy subsurface growth.

There were many other instances of R to S conversion but the examples quoted are sufficient to indicate the ease with which smooth colonies could be elicited from rough progenitors.

S to R conversion was also apparent on both liquid and solid media, but was less frequently observed as a complete change, and more often intermediate types were observed.

A culture from Sauton's broth that had been previously grown on normal serum-modified Sauton's medium was plated, and two rough colonies appeared, one of which is shown in figure 4.

A culture from broth, that had previously been two generations on normal serum-modified Sauton's medium, produced on plates both rough and smooth colonies, and each type produced pure cultures on replating.

After four generations on normal serum-modified Sauton's medium and two on the Sauton's medium without serum, an original Avian S culture produced a stiff pellicle growing over clear liquid. Other instances of that type of growth on the part of originally Avian S cultures were observed.

Animal inoculations showed four significant characteristics. The smooth and rough strains received from Dr. Kahn and those dissociated by us killed rabbits in widely disparate lengths of time; the smooth in

less than one month, the rough in from one to six months. The type of lesion produced was different, as has been so well described by Dr. Petroff (Winn and Petroff, 1933); the smooth often killing before macroscopic lesions were produced, and the rough causing large confluent caseous abscesses in all organs not excepting the kidney in many animals. Cultures were recovered with ease, and the same colony type was obtained from the animal as was injected into it. The fourth characteristic developed later in animal-passage experiments. The avian strains when received were but slightly pathogenic for susceptible guinea pigs, and not for others in 1-mgm. doses. Later 0.01 mgm. produced pulmonary tubercles after intraperitoneal inoculation though not death within two months. Only three passages were required to develop the marked increase in virulence. The avian strains seem to exhibit dissociation phenomena readily.

3. DISCUSSION

A variety of causes may have been responsible for the several reports of *BCG* causing death in guinea pigs.

(1) The strains of *BCG* received by the earlier investigators may have been less stable. Reports of virulent *BCG* were more numerous in the '20's than more recently.

(2) The strains may have differed in the extent of the early lesions produced. Griffith (1932, a) emphasized the toxicity of comparatively large inoculations of *BCG*. Zlatogoroff, Tzeknovitzer and Koschkin (1926), considering the acuteness of shock induced by large numbers of digested bacteria, used an abscence of the symptoms of toxicity as a criterion of increase in virulence.

(3) A strong presumption that is difficult to test either on published protocols or on our own work, is that a superinfection is more fatal in an animal loaded with *BCG* organisms. Of those animals in our experiments that died with an obvious bacteraemia from non-acid fast types or from bacterial pneumonia, 70 per cent had received comparatively large doses of *BCG* (10–112 mgm.), and a slightly differently composed 70 per cent died within 40 days after inoculation. The route of inoculation of *BCG* undoubtedly controls the distribution and extent of the early tubercles, before regression and resorption have been accomplished. If another cause of death supervene when the tissues seem full of tubercle bacilli a misinterpretation is difficult to avoid. Hormaeche (1930) used streptococcus infection in *BCG* animals in attempts to develop a virulent

substrain. Lowered host resistance through bacterial infection has not been successful in developing a strain of virulent *BCG* when confirmation for that idea was sought by others (Nelis, 1931; Moreau, 1931) nor have cultures recovered from our animals dying of intercurrent infection proved to be virulent.

(4) A most potent cause of undoubted generalized tuberculosis in laboratory animals is spontaneous infection. The lack of cultural controls on cases of this sort must have led to a misinterpretation of the cause of death. It is becoming more and more widely recognized that spontaneous infection, or cross-infection, does occur in animal houses (Griffith, 1932; Okel and Parish, 1928; Kolle, 1932; Cummings, 1932, b).

In the New York City Research Laboratory two *BCG*-inoculated animals were found to have extensive tuberculous lesions. From one a virulent bovine-type tubercle bacillus was recovered and from the other a human-type strain. Dissociation could not account for two contemporaneous instances of that sort, and the probability of cross-infection under the conditions then prevailing is very strong, especially since animals with advanced virulent bovine and human tuberculous infections were in the animal house at the same time.

Laboratory accidents are difficult to rule out. The avian infection in our group was traced to some error occurring during planting both *BCG* and avian bottle cultures in the same hour with the same equipment set-up. A substrain recovered from animals inoculated with a supposed pure culture of *BCG* grown on liquid medium containing anti-*BCG* serum proved to have the ability to produce progressive disease in subinoculated, that is, second-passage animals. By comparative animal pathogenicity studies and colony morphology the capacity for virulence was proved to be resident in tubercle bacilli of an avian type, resembling closely the avian rough we had been using in other studies. The first evidence was in favor of the presumption of the production of a *BCG* substrain that was virulent. Conclusive studies point to the assumption that the originally inoculated animals received a mixed culture. Comprehensive cultural studies are certainly indicated when dissociation seems to have produced sudden marked changes apparently from one type of strain to another type. The experience of Drs. Sasano and Medlar seems to us to have been most likely caused by a similar error rather than by cross-infection. The fact of a laboratory accident in the Luebeck disaster has been established. (*Luebecker Gutachten, Ztschr. f. Tuberk., 1932, 64.*)

The reports of finding generalized tuberculosis in laboratory animals following *BCG* inoculation have decreased in recent years, but frequent references are made to articles in which *BCG* is described as dissociated or in which *BCG* is spoken of as a potential pathogen. Though they have been unable to secure a repetition of their results, Doctors Medlar and Sasano still refer (1933) to their virulent strain as having been dissociated by three successive transplants on Sauton's liquid medium containing 10 per cent normal serum (1931).

The majority of those who have worked with *BCG* in animals have drawn mutually confirmatory conclusions: that lesions are produced, regularly at the site of inoculation and occasionally in adjacent lymph nodes or in organs, depending largely on the route of inoculation; that is, after intravenous or intraperitoneal and frequently after subcutaneous inoculation, bacilli may be found by microscopical examination of the organs, such as liver, spleen and lung; but that the lesions are regressive in nature and tend to heal; are much less pronounced at six months than at two, and ultimately disappear in varying lengths of time (Remlinger and Bailly, 1927; Okel and Parish, 1928; Fujioka, 1928; R. Kraus, 1928; King and Park, 1929; E. Piasecka-Zeyland, 1929; Kirchner, 1929, a; Lange and Clauberg, 1929; Gerlach, 1930; Neufeld, 1930; Boquet and Nègre, 1930; Togunawa and Larionowa, 1930; Griffith, 1932; Birkhaug, 1933).

Dreyer and Vollum (1931, b) reported that about 5 months after inoculation with *BCG* the majority of blood cultures were sterile. Tubercle bacilli belonging to virulent bovine and human strains do not remain in the blood-stream of laboratory animals long after inoculation, although they may reappear intermittently or after the disease process becomes extensive (Corper and Damerow, 1933). Mishulow and Park (1932, 1933) found that the intravenous route of inoculation was more apt to produce regular bacillaemia. Griffith (1932, a) also showed dissemination of bacilli after inoculation.

Some workers have reported that most of their experimental animals showed regressive healing lesions, but that a few showed extension of lesions and some animals died of generalized tuberculosis. Lange and Lydtin (1928) reported a small percentage of progressive tuberculosis following *BCG* inoculation. Three of Malkani's (1929) 46 animals showed progressive disease, two dying of generalized tuberculosis. Watson (1928) emphasized the small, though not the smallness of the percentage of his experimental animals which showed extensive lesions on

autopsy. Lurie (1932) reported some early deaths and some whose lesions were almost completely resolved in four months. Hutyra (1929) found cases of progressive lesions. Gerlach's (1927) report of non-progressive *BCG* infection was questioned by Nobel (1928), who endeavored to show that some of Gerlach's animals as well as his own showed progressive lesions. Gerlach (1930) reported one second-passage guinea pig that developed generalized tuberculosis after his research had been concluded. He tried to cause a repetition of that event by successive passages, but could not. Only the one case occurred in his experience. Other workers suggest spontaneous infection as the cause of the small percentage of generalized tuberculosis found in *BCG*-inoculated animals (Okel and Parish, 1928; Shroeder and Crawford, 1929; Kolle, 1932, p. 201). Feldman (1932, b) emphasized the frequency of microscopic lesions in tissues other than at the site of inoculation, but found all lesions incapable of conferring disease on subinoculation. He considered the extent of the disease process to be dependent upon the degree of resistance of the individual animal. Uhlenhuth and Seiffert (1930) said that progressive disease developed in an occasional animal as a corollary to lower natural immunity than is generally found. Gerlach (1930) said that the reaction shown by small animals to the *BCG* was influenced rather by the individual characteristics of the animal and by the age of the culture than by the size of the dose.

Notable research into the comparative pathology of induced *BCG* and other tubercle-strain infections has been reported by Lurie (1932) who worked with rabbits, and Schilling (1930) who worked on the pathology also of subsequent infection with a virulent strain. Both reported a multiplication of *BCG* in the body and the formation of typical tuberculous changes but no necrosis of the granuloma in *BCG* infections. *BCG* and human-type bacilli are usually effectively destroyed within epithelioid cells of all organs of the rabbit.

Maximow (1928) studied the changes in tissue-culture when *BCG* and virulent bovine bacilli were inoculated. He did not observe a destruction of cells, nor any evidence of toxic action on epithelioid cells and fibroblasts by *BCG*, but the bovine bacilli attacked both types.

As has been said in a previous section, attempts to regain a culture by digestion of animal tissues were most often successful when an abscess at the site of inoculation was the source of the material planted. However, similar lesions in 38 animals did not enable us to recover the strain by similar methods. When studying the bacteriology of the pus of *BCG*

abscesses, Parisot, Fernier and Saleur (1929) found that it was sterile on culture although acid-fast forms were found in smears. They found the lesions incapable of infecting subinoculated animals as well. Our results show more success in regaining cultures, but when the cultures were used as passage strains their ability to infect animals was very much the same as that of original *BCG* cultures. The strains were eventually lost in subsequent passage groups of guinea pigs.

The percentage of recoverable cultures when the substrains were of *BCG* origin (17.2 per cent) was in marked contrast to the ease with which cultures were recovered from animals inoculated with a virulent bovine strain (100 per cent) or with the avian strains used by us (96 per cent).

It is significant that cultures recovered from *BCG*-inoculated animals tend to have a colony morphology like those of our unmanipulated *BCG* stock strain, coarsely coiled or crater coil on egg media, and coil or pile with smooth high pedicles on Bordet-Gengou medium. In only one case was a flat-type colony recovered after flat colonies were administered, and this characteristic was lost in subsequent passage through animals.

The passage of *BCG* strains through animals has been reported as effective in developing a virulent substrain (Korschun and collaborators, 1927; Watson, 1928; Petroff, 1929) and as unsuccessful in demonstrating that *BCG* has the possibility of acquiring virulence by Tiedeman (1930), Griffith (1932) and Birkhaug (1933) among others. Animal passage has not been effective in raising the virulence of another attenuated strain, R1 (Cummings, 1932; Willis, 1933). Willis gives a good bibliography on animal-passage experiments.

Since we designated pathogenicity in animals as the only criterion of effective dissociation of the *BCG* strain, all strains that were tested by animal inoculation, and those repeatedly recovered from animals thus became passage strains. Repeated residences in the animal body did not appear to adapt the strain to that environment, and the problem of when to kill an animal in order to recover the strain could be answered only by guess. The viability of *BCG* in the body of the guinea pig and rabbit seems to depend partly on whether a sizeable abscess is formed at the site of inoculation, but even a large tumor at that point was not regularly the source of cultivable or subinoculable bacilli. The conclusion from our studies is that animal passage was not successful in inducing in a strain the development of a resistance to the destructive body environment sufficient to ensure its viability in, or recoverability from, the host tissues.

Viability and virulence were shown to be independent characteristics *in vitro* by Corper and Cohn (1933), but in pathogenicity studies a strain must first be adapted to the host tissue before it can cause progressive disease.

Dissociation of *BCG* is essentially R (rough) to S (smooth) reversion. We may assume that S to R dissociation took place when *BCG* was developed from an originally highly virulent bovine strain isolated by Nocard. The possibility must be considered that the degradation in its antigenic complexity, as found by Rice and Reed (1932, c) in R strains of tubercle bacilli, may be irreparable.

BCG is dissociable into apparently rough and smooth substrains on the basis of colony morphology.

BCG colonies on Petroff's and Loewenstein's egg media and on Bordet-Gengou medium may be of several distinct types, unmistakably identifying them as of the strain and scarcely to be confused with colonies of other types of tubercle bacilli. The fact that those eight or so types may be present in plates seeded from glycerinated-bile-potato or synthetic fluid media, even in the first generation on egg, argues for very ready dissociation indeed, or for the more logical assumption that these primary colonial types do not represent dissociation.

From the rough coil colony of the largest incidence in an undissociated *BCG* culture there may be produced by selective colony fishings a definite progression through horizontally arranged coil colonies, to broken-coil (cross-furrowed) and beaded-surface colonies and ultimately to an extremely flat colony with a tiny raised button centre that is quite transparent and finely grained from the centre to the fairly regular spreading margin. These last colonies reproduced their own kind on subsequent seedings. They have been obtained in our experience from successive fishings of flattened intermediates; not from passage of the strain through animals nor by growth deep in broth nor on the surface of liquid media.

The extremely flat transparent colonies are much more easily emulsifiable in saline solution than original *BCG* cultures, but less easily emulsifiable than growth from a virulent bovine culture. Our strain was maintained for more than a year, but was lost on artificial media, even though several attempts were made to rejuvenate it by successive transplantings. A strain recovered from one of the guinea pigs of the first set inoculated with these flat colonies was also flat, but the characteristic was lost on subsequent inoculation and the strain was not recovered from the fourth series of subinoculated animals.

EXPLANATION OF PLATE

Magnification, approximately 1×, except fig. 22 which is 3×

Fig. 1. Human strain, H3, Loewenstein plate after recovery from guinea pig.

Fig. 2. Sasano-Medlar strain, bovine type, after one plant on homologous anti-serum. Margin is less regular than when recovered from animals. Petroff medium.

Fig. 3. Sasano-Medlar strain after four successive transplants on glycerine-bile potato. Pigment has deepened. Margin is less delicate. Petroff plate. This culture showed some attenuation of virulence.

Fig. 4. Avian smooth strain showing one "R" colony on plate after 2 "generations" on Sauton's media, one containing normal rabbit serum. Loewenstein medium.

Fig. 5. Avian rough strain showing one "S" colony after 6 "generations" on liquid medium, 2 with normal rabbit serum. Loewenstein medium.

Fig. 6. Recovered from rabbit given *BCG* substrain grown on normal human serum. Loewenstein medium.

Fig. 7. *BCG* colonies growing on Bordet-Gengou plates seeded for the 8th consecutive time with flattened margins of colonies. Coils subordinated.

Fig. 8. *BCG* "broken" coil colony from culture on anti-*BCG* serum. Loewenstein plate.

Fig. 9. *BCG* coil colony from culture 5 times transplanted on media containing anti-*BCG* serum. Petroff medium.

Fig. 10. *BCG* crater coil colonies on Bordet-Gengou medium showing slight tendency to spread. *History:* 5 "generations" on plates seeded from flattened colonies, 6 on liquid media containing normal human serum followed by 3 more selectively fished seedings on plates.

Fig. 11. *BCG* on Petroff medium after 5 "generations" on plates, 8 on liquid media containing normal human serum and 4 more on plates.

Fig. 12. A recovered culture, proved nonvirulent on passage; originally *BCG*. *History:* plated 5 times; subplanted on liquid media 7 times; in animal body 36 days. Flat colonies in digestion tubes plated.

Fig. 13. Recovered from guinea pig inoculated with 5th generation normal serum subculture of *BCG*. Not recovered from subinoculated guinea pigs. Loewenstein medium in Petroff flask.

Fig. 14. Recovered from guinea pig given deep broth subculture of *BCG*. Bordet-Gengou medium.

Fig. 15. *BCG* after 12 subcultures on normal human serum. Bordet-Gengou medium.

Fig. 16. *BCG* after subculture on anti-*BCG* serum. Loewenstein medium.

Fig. 17. Substrain of *BCG* after selective subculturing on solid medium for flat colonies and 5 subsequent subcultures on anti-*BCG* serum. Petroff medium.

Fig. 18. First subculture on Petroff medium from glycerine-bile-potato culture of *BCG*.

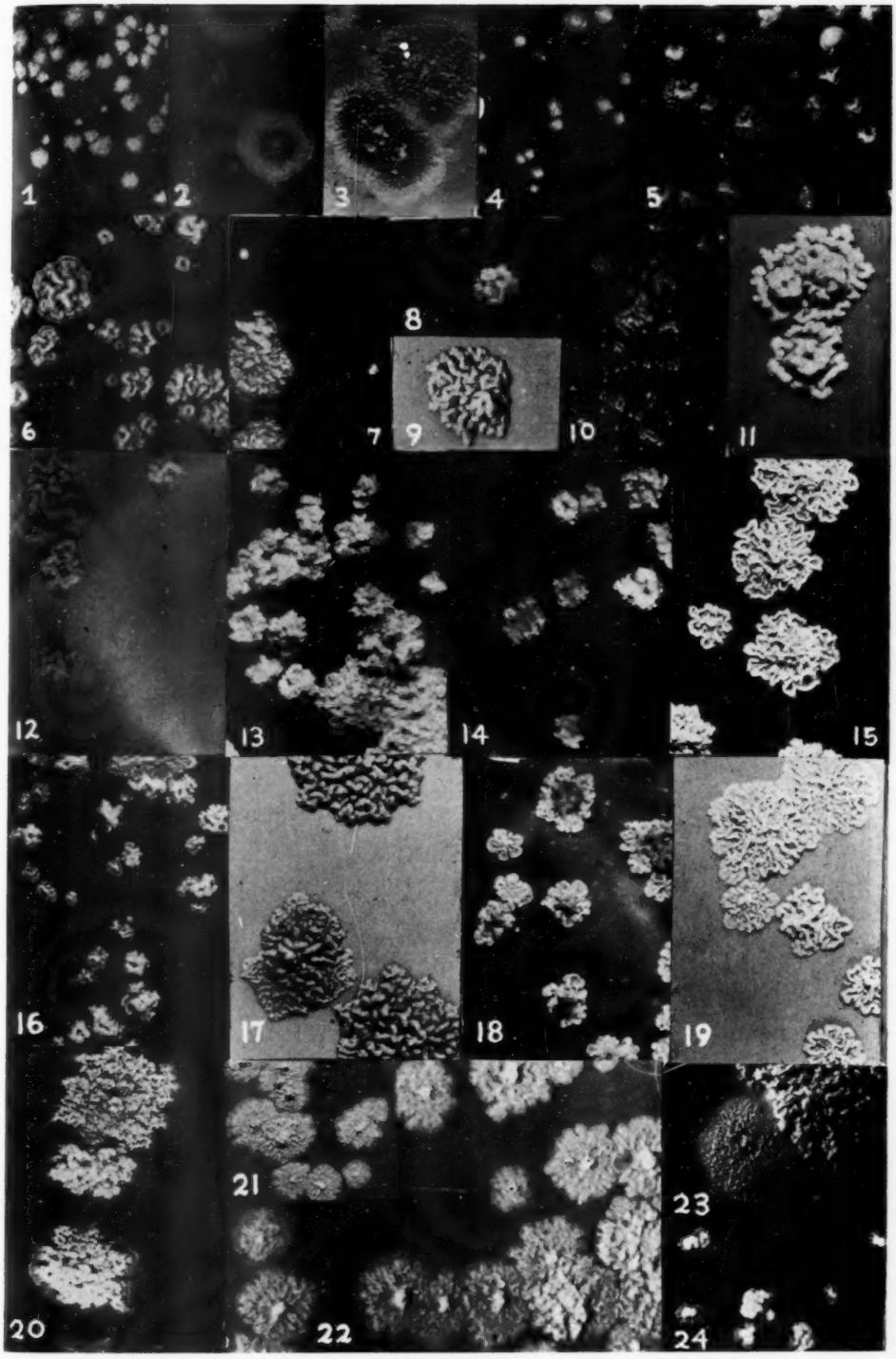
Fig. 19. One of 2 colony types of which figure 23 is the other, from a *BCG* strain subcultured on solid medium 10 successive times, each seeding made from a flattened margin. Petroff medium.

Fig. 20. Seventh *BCG* subculture by seeding flat colony fishings on solid medium; in a series separate from that of figure 19.

Figs. 21 & 22. Colonies in a later culture of the same selectively fished *BCG* series as figure 20. Nonpigmented, easily emulsifiable, nonvirulent. Petroff medium.

Fig. 23. See figure 19.

Fig. 24. Sister colonies of the parent colony of figure 22.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The Sasano-Medlar strain used by us, which they report as of *BCG* origin (1931), grew with extreme difficulty on glycerinated-bile-potato. After the fourth subplant, the colony on egg had not changed in character (figures 2 & 3), though the time required for a given dose to produce death from generalized tuberculosis was lengthened.

The Mycobacterium of avian tuberculosis is exceptionally susceptible to dissociation into rough and smooth types marked by a most distinct colony morphology. Rough and smooth strains developed from selected single cell cultures gave many instances of R to S and S to R changes in the short period of four months by the several laboratory methods of cultivation; for example, on Proskauer and Beck's synthetic solution A, on Sauton's synthetic liquid medium containing 10 per cent normal rabbit serum, by seeding on egg plates and fishing selected colonies for propagation.

Strains of avian tubercle bacilli vary greatly in their pathogenicity for rabbits and especially for guinea pigs. The primary series of animals which received inoculations of R types regularly did not develop progressive tuberculosis, and the culture, usually recoverable, was obtained also in the R form. Similarly, if S-type colonies were inoculated S cultures were recovered. But avian strains in these separate experimental series were shown to increase rapidly in virulence on passage through animals, so that even 0.1 mgm. produced extensive macroscopic lesions in guinea pigs.

4. CONCLUSIONS

1. *BCG* did not acquire virulence in laboratory culture on liquid media containing either normal human serum or homologous antiserum or in the depths of nutrient broth or by successive selection for propagation of smooth-appearing colonies on solid media or by repeated animal passage.

2. The variation that we saw develop in colony morphology under different environmental conditions was not accompanied by enhanced pathogenicity.

3. A virulent bovine-type strain was found to be resistant to laboratory modification, but some attenuation in virulence was produced together with a slight change in colony morphology, with the appearance of some characteristics usually associated with the rough variant.

4. Avian strains were found to be labile, developing changes in colony morphology in both S to R and R to S directions, and with also some

marked variations of each type, together with accompanying changes in pathogenicity under environmental conditions similar to those imposed on *BCG* strains.

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REINFECTION AMONG TUBERCULOALLERGIC DOCTORS AND NURSES AT FITZSIMONS HOSPITAL[1]

WILLIAM C. POLLOCK[2] AND JAMES HEDGES FORSEE[2]

This study consists of a survey of 227 medical officers, 19 dental officers and 518 members of the Army Nurse Corps on duty at Fitzsimons Hospital during a ten-year period. All individuals of the group were classed as tuberculoallergic in that we were able to demonstrate X-ray evidence of past invasion by tubercle bacilli. X-ray evidence of tuberculous infection, in the vast majority of instances, consisted of a Ranke's primary complex, while in a few instances there was also evidence of a subsequent reinfection.

Group studies, as a rule, are not found to be 100 per cent tuberculoallergic and, since our group is so reported, some explanation is deemed advisable. We believe that such explanation lies in the fact that we are dealing with an older age-group, consisting of individuals who are either college and medical-school graduates or graduates of nursing schools. In addition to this they have had from a year or so to fifteen years' hospital experience. In all individuals of the group there must, of necessity, have been repeated exposures to active tuberculosis. Conclusions or results of a survey of this character should necessarily differ from one made upon a group which includes noninfected individuals (nonimmunes).

Since all of the group present X-ray evidence of a tuberculous pulmonary infection, they are classed as tuberculoallergic, realizing, of course, that this tuberculobiological state, as is true of any relative immunological reaction, exists in varying degrees. It exists in varying degrees in different individuals and in the same individual, as influenced by the factors of time and reinfection.

Authors have recently reported the results of their observations in regard to the danger or infection of nonimmunes, during or following their period of required duty on tuberculosis services. Further study of this group who developed tuberculoallergy while under observation

[1] Published by permission of the Surgeon-General, U. S. Army.

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showed that a certain number later developed a reinfection type of tuberculosis which in some instances was of a destructive character. This sequence of events, together with a comparative estimation of the severity of initial infections and reinfections, created doubt as to the value of tuberculoallergy in human tuberculosis.

Whether a primary tuberculous infection which heals but afterward renders the human host allergic, and therefore capable of reacting to further invasion by an altered tissue response, is of a protective character and of value or detrimental because of this altered response, has apparently again become an issue. It is not our purpose to attempt to solve this problem, as certain phases of the complex problem are so little understood that it is probably unwise to even attempt their discussion. We hope that our observation of 764 tuberculoallergic individuals, who have been assigned to duty at Fitzsimons Hospital during the past ten years, may be of some value in estimating the danger of reinfection of such individuals when exposed to continuous exogenous sources of infection by tubercle bacilli of varying virulence. Results must not be considered entirely from a standpoint of exogenous reinfection, but of endogenous reinfection under continuous exogenous exposure.

As stated, certain phases of this problem are complex, and not thoroughly understood, and the problem is further complicated, in clinical studies, by aetiological factors often unknown to the observer. Some aetiological factors of clinical studies are not controllable factors, and for this reason certain deductions from controlled animal experiments possibly should be accepted notwithstanding our failure to note the finding, as a constant observation, clinically. It is possible that expressions of opinions, substantiated by controlled accurate experimentation or clinical observations, may result in the correlation of constant and positive observations, with the ultimate result of better and more widespread understanding of the quality and quantity of immunobiological reactions in tuberculosis. To illustrate the diversity of opinions upon this particular subject, we have selected the following paragraphs from various articles.

Myers (1) asks the question, "Is it better to have a positive or a negative tuberculin reaction?" He states, "There are extant in the literature numerous statements to the effect that those who react positively to tuberculin have immunity to tuberculosis. Since there is no accurate test for immunity, a good deal of what has been said in the past regarding it was based on personal opinion."

Stewart (2) expresses his opinion as follows:

The ability of non-allergic individuals to cope successfully with initial infections of varied doses of tubercle bacilli such as are commonly received in average human experience apparently is so prevalent in man that but few can identify the time they acquire the primary type of tuberculosis by any known illness or impairment of health directly attributable to this disease.

He states further,

Follow-up studies over a period of 10 years at Lymanhurst indicate that primary tuberculous infections are distinctly detrimental in that they alter the normal resistance to tuberculosis present in the uncontaminated human body in such a manner that instead of again being able to experience the benign primary type of tuberculosis, the patient is doomed thereafter to develop consumption if successfully reinfected from exogenous or endogenous sources.

Krause (3) states,

The allergic state is recognizable only through the appearance of the allergic reaction. This reaction is marked characteristically by elements of acute tissue response, by features of acute inflammation. If intense enough, the reaction will result in tissue necrosis (caseation), and there is reason to believe that the necrosis, a destructive phase of tuberculosis, is brought about by the allergic reaction.

He goes on to say,

But involved in the allergic reaction is also an accelerated proliferation of cells that build up nodular tubercle, and as one end-result of the reaction, must be regarded as enhanced fibrosis of the tuberculous process. Accordingly, the allergic reaction is seen to be responsible for all the acute manifestations of tuberculosis, and when so considered it must be viewed as a potent contribution to pathogenesis.

In speaking of immunity, Krause states,

When subjected to careful, controlled observation specific immunity exhibits itself as follows: Infected animals of experiment, when exposed to reinfection, suffer as a result of the latter, a tuberculosis that for a long time is relatively localized, that (after the subsidence of the early acute phases) takes on the anatomico-pathological features of chronicity (fibrosis, etc.), that then spreads with great slowness, if at all, and that leads to death only after a much delayed evolution of the infection (reinfection).

He states that

The course of events is in striking contrast to what goes on in the normal nonimmune animals for when the first evidence of tubercle comes to light tardily, disseminating pathological changes appear with but slight interruption or delay, and generalized tuberculosis carries off the animal within several weeks, or a few months at the latest.

Medlar and Sasano (4) in their experimental work found considerable variation in histopathology. They list the following influencing factors:

1: The age of the host and its relative susceptibility or resistance, natural or acquired, to infection.
2: The degree of virulence of the infectious agent.
3: The route of infection.
4: The relative amount of infectious material inoculated.
5: The time elapsed after infection.

They state, "We are of the opinion that a considerable amount of erroneous interpretation of the pathogenesis of tubercle and of the essential difference between primary and secondary infection has appeared in the literature in the past because of failure to properly consider the interplay of factors given above." They were able, by use of virulent tubercle bacilli, to produce cavitation in normal nonallergic animals. They were able to produce microscopic abscesses within five days which they consider occurred prior to an allergic state.

Myers (5) in discussing types of tuberculous lesions concludes, "A positive tuberculin reaction, indicating allergy resulting from first-infection type of tuberculosis, is a definite liability, since the destructive forms of tuberculosis do not ordinarily develop in nature in its absence. Therefore, the longer it can be postponed, the better."

Heimbeck (6) concludes, "The susceptibility to tuberculous infections among student nurses with negative reactions to the Pirquet test who are exposed to tuberculous patients is excessively high (29.6 per cent), in contrast with a relatively high resistance to tuberculous infection among student nurses with a positive reaction to the Pirquet test (2.6 per cent)."

Bushnell (7) states, "Acquired immunity, while not sufficient in many cases to prevent extension of disease in the injured tissues in continuity with the primary focus, is sufficient to counteract new infection from without."

Pinner (8) is of the opinion that, "Only an allergic animal can be killed within a brief time by an infection with tubercle bacilli. Only in allergic soil does an infection ever cause acute and toxic conditions with their concomitant grave clinical picture; only in allergic tissues does an infection ever cause acute exudative foci with rapid caseation and tissue destruction." He states that "Fibrosis seems to occur only in allergic soil and that, healing in a non-allergic organism cannot be observed, because the focus to be healed must have produced allergy already." He again states, "It seems that a rapid resorption of exudate occurs only under the same conditions under which it develops, namely, high allergy. Whether competent fibrosis develops more readily under conditions of a low degree or high degree of allergy is open to discussion."

Ryder (9) thinks it improbable that acquired immunity is an important favorable factor in human tuberculosis, and probable that "natural," innate, or hereditary immunity is a very important one. "Especially in pulmonary tuberculosis, the altered tissue reaction following first-infection seems to favor the development of disseminated ulcerative phthisis."

Pottenger (10) in discussing primary infection states, "Either the infection is so severe that a generalized tuberculosis occurs, which results in quick destruction of the patient, or the infection is so slight that it either heals of its own accord or, failing to heal, remains in a state of quiescence, without producing symptoms." In speaking of reinfections he says,

> The tuberculosis due to reinfection is chronic in nature, being a disease which is implanted in immune soil. The term immunity in connection with tuberculosis must always be considered as meaning a relative immunity, and as being variable under varying circumstances and stresses of social and economic life and under conditions which accompany diseases.

Ornstein, Ulmar and Ditler (11) in discussing *Benign Acute Tuberculosis,* state that in their opinion,

> The type of reaction depends upon the relationship between the dosage and virulence of the super-infection and the reaction of the cells of the host; in other words, upon the relationship between the tubercle-bacillus protein and the threshold level of the body cells to allergic stimulation. If the threshold level is high, a comparatively large dose of bacilli will be required to produce the allergic reaction. On the other hand, a person who has a low threshold level, that is, a person who is very allergic will react to a minute dose of tubercle bacilli with an intense allergic or serous exudative type of reaction.

Meyerding (12) concludes that in the average case a minimal (first or childhood type) infection will usually resolve and heal with a calcareous deposit. The secondary infection in the average case in which there has been an early first infection produces localized destruction which may end in metastasis to other parts. He thinks that if one must have a tuberculous infection, it would be best to have the minimal, first or childhood, type of infection early so that when and if the secondary infection should occur the destruction might possibly be more gradual.

Willis (13) states,

> We know that the animal which is infected with the tubercle bacilli is in some degree specifically protected against the disease for which that germ is responsible. We know that the immunity which such an animal possesses is only relative or partial and that the size of the reinfecting dose is an important factor in determining the competence of the immunity.

The brief digest of the few opinions enumerated above clearly demonstrates the differences of views in regard to the character and quality of tuberculoallergy. A more extensive critique of the literature upon this subject may not clarify the question but would rather tend to add somewhat to the existing confusion. It is possible that additional reports of clinical studies and controlled animal experiments will not add to the confusion, as conclusive opinions should result from the consideration of extensive data.

We believe that tuberculoallergy which develops during the initial invasion of the host by tubercle bacilli serves, when maintained at an optimum level, as a protective quality. This protective quality hinders or prevents exogenous reinfections and may limit to a chronic process an endogenous reinfection sufficiently massive and virulent to produce widespread disease with final annihilation of the nonimmune host. This is true because tuberculoallergy is so soon followed by the development of a tuberculoimmunity. These protective qualities are relative or partial in regard to their immunizing power but, in general, are sufficient to protect the salubrious physician or nurse assigned to duty in a well-regulated hospital for tuberculous patients. Under the same conditions nonimmunes rapidly become infected and in instances become ill of tuberculosis. Whether the nonimmune develops a benign disease or becomes ill of manifest tuberculosis, depends upon many factors. Influencing factors are dosage and virulence of the invading bacilli, age and natural physical resistance of the host, but these are certainly influenced by many

other factors attendant on so complex an organism as the human host. Such factors as physical strain and mental stress are immeasurable and often uncontrollable factors, influencing infection as well as the cause of the disease. Probably more important than factors already mentioned is that of repeated reinfections, especially those that occur when allergy happens to be at an unfavorable level.

Authors have attempted to present the primary invasion by tubercle bacilli as always being a benign disease, whether in the child or non-immune adult. Their description of the invasion would lead one to believe that the infection occurs unknown to the host, since it produces few or no symptoms and heals by calcification. They lead us to believe that this benign process, apparently so harmless in itself, produces allergy which thereafter dooms the individual to a destructive character of the disease when successfully reinfected from exogenous or endogenous sources.

We do not believe that all primary tuberculous invasions are benign in character. Fortunately, a great many of such infections do prove to be benign. The course of the disease, however, may vary from a benign type when influenced by factors present in the host as well as in the bacilli themselves. We know that reinfection tuberculosis is extremely variable in its manifestation and in its course. It does not seem logical to attempt to explain all of such variations entirely upon the basis of immuno-biological reactions without consideration of other factors. If other factors are considered, then these same factors are to be considered when studying both the immune and the nonimmune for the same factors are of influence in both instances.

Sweany (14) believes these primary lesions in the adult do not conform to the established doctrines of primary infection.

Blumenberg (15) suggests that primary infections must be considered from the standpoint of the various "courses" resulting from the qualitative and quantitative aspects rather than consider only one type running through a certain set of "stages."

Sewall, *et al.* (16) have shown that the effect of large dosage in experimental animals tends to prove more of a reinfection type of lesion.

Meyerding states, "A super-infection on a non-reactor, or in so-called virgin soil, together with accompanying "stress," as a rule does not permit the usual resolution of the first or childhood type of tuberculosis infection. It results instead in a continuous pathologic condition proceeding without pause from the first into the destructive type."

As to age of the host, Ghon noticed a gradual decrease in the progressive cases from the 1st to 14th year, with evidence of healing increasing with age. According to Opie (16), "In the first two years of life there is almost no tendency to heal; the lesion on the contrary is progressive and tends to spread by caseation." In such instances, we are dealing with uncontrolled repeated reinfections at a time when allergy is not maintained at an optimum level. This is true whether the host is an infant, member of a primitive race, or a nonimmune medical student. In discussing this observation in infants and members of primitive civilizations, Krause states, "They are expressions of relatively heavy repeated infections with tubercle bacilli of body tissues that are extraordinarily sensitive because little time has elapsed since the primary infection and allergy has not had time or opportunity to wane." Krause has repeatedly spoken of the rise and fall of allergy as influenced by reinfection or lack of infection.

Gelien and Hamman (18) from clinical observations expressed their belief in a fluctuating hypersensitiveness with sharp rises upon reinfection (metastatic) in the course of human disease.

Kraemer (19) pointed out that there is a fluctuation of hypersensitiveness in tuberculosis.

Willis (20) in his study upon guinea pigs concluded, "It is shown that a scarcely detectable allergy in old and healing infection is immediately restored to old high levels by fresh reinfection."

Primary tuberculous infection may produce a benign disease process with the ultimate formation of Ranke's primary complex so clearly shown upon the X-ray film. Primary infection followed by repeated reinfections from known or unknown sources may produce a destructive type of tuberculosis within a short period. It is the factor of untimely repetition of the infection which endangers the infant or the nonimmune adult assigned to duty on a tuberculosis service. Nonimmunes subjected to constant reinfection are our future candidates for tuberculosis wards, in that during the period of reinfection allergy is caught at an unfavorable level, immunity is depressed and the individual's relative protection is either decreased or in instances overwhelmed. The same situation may result from a massive, virulent first infection, for under these circumstances there may develop a clinical-pathological picture simulating reinfection tuberculosis. Under these circumstances there may be reinfections from the site of the first invasion and since allergy follows so rapidly after a successful initial invasion, the reinfections occur in the presence of a rising allergy.

Many speak of the fine example of healing so frequently observed upon X-ray films in cases of first infections. There is a dense, well calcified parenchymal lesion which often remains unchanged throughout life. This calcified node may remain unchanged in the presence of active reinfection in other portions of the same lung. This excellent example of healed tuberculosis often, if not always, takes place in the presence of allergy, for allergy develops so soon after invasion that certainly healing processes of first infection go on to completion in the presence of this quality. In smaller first infections of nonimmunes, the end-result is often an excellent example of healing. In immunes, we often observe evidence of reinfection healing of smaller invasions which to all appearances present a parenchymal calcified node or nodes just as securely healed. Not all invasions of tubercle produce destructive disease in the immune. Animal experiments and clinical observations bear out these facts and it is for these reasons that tuberculoallergic individuals who possess a relative immunity to tuberculosis are more suitable to perform duty on tuberculosis services. They do not under ordinary methods of precaution become ill of tuberculosis as the result of repeated exposure to exogenous sources of reinfection. Tuberculoallergic individuals develop manifest tuberculosis because of endogenous reinfection and whether or not this should occur depends upon factors already mentioned. During the past ten years 227 medical officers, 19 dental officers and 518 nurses have served as members of the staff at Fitzsimons Hospital. Table 1 shows the number of each class who developed tuberculosis either during or subsequent to their tour of duty at this hospital.

TABLE 1

Incidence of tuberculosis among medical officers, dental officers and nurses at Fitzsimons over a period of 10 years

CLASS	TOTAL NUMBER	NUMBER DEVELOPING TUBERCULOSIS	PERCENTAGE	NUMBER WITH LATENT DISEASE UPON JOINING THE STAFF
Medical	227	4	1.7	1
Dental	19	1	5*	1
Nurses	518	8	1.5	6

* The high incidence as to percentage among dental officers, of course, is explained by the small number of this class doing duty here. In regard to medical and dental officers, the following data are considered pertinent prior to any discussion as to the significance of duty here as an aetiological factor of their disease.

Case 1: Age 26. Joined the staff as a medical officer July 1, 1930. Upon examination, including stereoscopic X-ray films, he was found to have had a first-invasion type of tuberculosis, consisting of a calcified parenchymal pulmonary lesion. No visible calcification in hilum lymph nodes. After eleven months of duty, which included duty on a ward for tuberculosis, Tuberculosis Service, he developed tuberculous pleurisy, serofibrinous in character, and later complicated by a tuberculous fistula in ano. Subsequent X-ray films revealed a very small subpleural parenchymal lesion of the upper lobe which healed by fibrosis. The officer had phthisiophobia and took extreme precautions against exogenous sources of infection. No history of childhood contact with open pulmonary tuberculosis.

Case 2: Now aged 41. Performed duty for a period of four years as a dental officer, most of his work being upon advanced cases of pulmonary tuberculosis. He returned to this institution as an advanced case of pulmonary tuberculosis with lesions of a destructive character with bilateral cavitation. Onset of his symptoms was in April, 1931, while on duty at a foreign post. X-ray upon joining the staff in 1922 showed a moderate amount of pulmonary fibrosis in the upper left lobe, considered to be completely arrested but with sufficient evidence of preëxisting disease to warrant a warning as to his mode of living. His mode of living at his foreign post was not of a protective nature and he developed an endogenous reinfection. His initially arrested disease had as its source of infection an open case of tuberculosis of his mother who died of the disease at the age of 38 years. It is believed that his duty subjecting him to exposure to tuberculosis while at this hospital was not the cause of his ultimate pulmonary tuberculosis. Sufficient evidence of possible future illness from tuberculosis was found and the individual warned prior to his exposure at this hospital.

Case 3: Age 25. Joined the medical staff July 1, 1930, and after 37 months of duty developed a tuberculous lesion in the 3rd lumbar vertebra. X-ray plate made in July, 1930, showed a healed first-infection type of pulmonary tuberculosis, as shown by a Ranke's primary complex. In addition to the calcified parenchymal lesion, there was present a minimal fibrosis extending well into the lung periphery. No family history of tuberculosis or other conclusive source of exposure during childhood. No change in chest plates from 1930 to 1933 inclusive.

Case 4: Now aged 34. Was on duty at this hospital from July 1, 1925, to September, 1926. First symptoms of tuberculosis were noted while on tropical service in 1929. X-ray of chest in 1925 showed a healed first-infection type of tuberculosis with some evidence of reinfection as shown by minimal

fibrosis. This case is thought to be a reinfection type of tuberculosis, endogenous in character, the result of strenuous service in the tropics. No history of childhood contact with pulmonary tuberculosis.

Case 5: Age 29. Although a member of the staff for a few months, had sufficient X-ray evidence of pulmonary tuberculosis that it could not be assumed that he contracted tuberculosis while here. He entered the service in 1924 and became ill of tuberculosis in May, 1927. Was retired and took a position in a civilian institution for tuberculosis, his duties causing his chronic process to become destructive in character. He was later readmitted and a thoracoplasty performed in 1932. He is now continuing his practice with his disease apparently arrested.

Table 2 lists the data considered pertinent when considering the incidence of tuberculosis among nurses.

Of the 227 medical officers, 4, or 1.7 per cent, developed tuberculosis. Two developed pulmonary tuberculosis, 1 tuberculous pleurisy and 1 tuberculosis of the spine. One medical officer had latent pulmonary tuberculosis upon joining the staff, which was sufficiently shown on X-ray film to warrant the conclusion that he had a reinfection tuberculosis which had become arrested. This leaves only 3 cases to be considered as contracting their infections at this institution. Of the 19 dental officers, the one becoming ill of tuberculosis had very definite latent tuberculosis upon joining the staff. In regard to the 518 nurses, 8 developed manifest tuberculosis. Six of this number showed X-ray evidence of healed or latent tuberculosis upon joining the staff. Prior to definitely diagnosing tuberculosis, 4 of the 8 had been hospitalized and observed for tuberculosis. Two nurses gave a positive family history of tuberculosis exposing them to open tuberculosis during early childhood. Among the nurses, this leaves for consideration the possibility of 2 cases becoming reinfected during service here.

A study of the data enumerated does not preclude the possibility that 2 medical officers and 2 nurses developed tuberculosis because of exogenous reinfection, endogenous reinfection because of continuous exogenous exposure, or endogenous reinfection because of other factors incident to their term of duty at a tuberculosis hospital. However, the evidence is in no way conclusive that such was the case. It would seem erroneous to conclude that these individuals developed tuberculosis because they were allergic to the invasion of tubercle bacilli while exposed to constant exogenous sources of infection. It seems more logical

TABLE 2

Incidence of pulmonary tuberculosis among 518 nurses at Fitzsimons Hospital
Incidence of 1.5 per cent

CASE	AGE	DUTY PERFORMED PRIOR TO DIAGNOSIS	HISTORY OF PRIOR EXPOSURE OR OF THE DISEASE ITSELF	DIAGNOSIS	DATE OF DIAGNOSIS	REMARKS
		months				
1	25	16	Under observation for tuberculosis in 1926	Tuberculosis upper lobe left, with small multiple cavitation. Lesions caseofibrous	June, 1930	X-ray and physical examination negative January, 1930. Reinfection type of tuberculosis
2	25	2	None	Tuberculosis upper lobes both lungs. Small cavity left upper. Lesions caseofibrous	August, 1926	On duty here in 1925. Transferred to another station. Developed tuberculosis 3 months later. Reinfection type of tuberculosis
3	34	18	Was hospitalized and observed for tuberculosis in 1927. Arrested lesions present in the form of fibrosis	Tuberculosis upper lobes both lungs with small cavities both uppers. Lesions caseofibrous	June, 1928	Transferred to another station. Had influenza in May, 1928. Reinfection type of tuberculosis
4	34	30	Pleurisy 1927. Latent tuberculosis by X-ray when she joined the staff	Tuberculosis both upper lobes with cavitation both upper lobes	September, 1928	Developed reinfection tuberculosis after 4 months of duty, as shown by X-ray plate
5	24	24	Observed for tuberculosis in August, 1932. None found	Tuberculosis upper lobe, left	February, 1933	Reinfection tuberculosis after two years of duty

TABLE 2—*Concluded*

CASE	AGE	DUTY PERFORMED PRIOR TO DIAGNOSIS	HISTORY OF PRIOR EXPOSURE OR OF THE DISEASE ITSELF	DIAGNOSIS	DATE OF DIAGNOSIS	REMARKS
		months				
6	27	36	One brother and one sister died of tuberculosis. Was closely associated with them from early childhood until 14 years of age	Tuberculosis upper lobe left lung with small cavity	January, 1933	Influenza in January, 1932. Was always below par physically following this. Tuberculosis discovered at annual physical examination January, 1933. Reinfection tuberculosis
7	25	44	No family history of tuberculosis. No former observation for tuberculosis	Minimal involvement of upper lobe left. No cavitation	May, 1933	Former plates showed small latent lesions. Reactivation of latent lesions
8	38		Mother, brother and sister died of tuberculosis. Observed for tuberculosis in 1926	Minimal involvement upper lobes both lungs	March, 1928	Duty at this hospital in 1926

to consider that since 223 medical officers, 18 dental officers and 510 nurses have remained well, it would certainly illustrate that the dangers of reinfection are minimal. Considering the group as a whole, we have 764 allergic individuals and, granting that the 13 persons who became ill did so because of service here, the morbidity rate would be only 1.7 per cent. This would be erroneous, however, for we must consider that only in 3 cases we were unable to demonstrate causative factors, which reduces the percentage to 0.39.

Comparing our figures to those reported by Myers and Heimbeck who reported the incidence of tuberculosis among nonimmunes, it would seem logical to assume that the dangers of exogenous reinfection are much less among individuals possessing specific tuberculoimmune reac-

tions. Our medical officers have been able to "carry on" in the presence of continuous exposure to exogenous sources of infection by virulent tubercle bacilli without developing manifest symptoms of tuberculosis. This has been possible because their relative immunity has been obtained and maintained by invasions of tubercle bacilli. First invasion and subsequent invasions, though necessarily haphazard in nature, have fortunately been of a dosage and virulence insufficient to produce manifest clinical tuberculosis of healthy individuals. On the contrary, these invasions have served to maintain immunobiological reactions at an optimum protective level. A few have not done well because they presented too extensive evidence of past tuberculous infections. In the presence of these latent or arrested lesions allergy, upon reinfection, ascended to unfavorable levels, and subsequent repeated reinfections from within, at moments so inopportune, converted tuberculoallergy, a usually protective quality, into a biological reaction detrimental to the host.

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BLOOD COUNTS IN CLINICALLY HEALED PULMONARY TUBERCULOSIS[1]

JOSEPH M. KURUNG

Many observers, including Solis-Cohen and Strickler (1911) and Watkins (1911), have held that an increase in the number of lymphocytes is evidence of a favorable prognosis in tuberculosis. Webb, Gilbert and Newman (1923) concluded from an analysis of 400 cases that a high lymphocyte count is usually found in patients with apparently cured pulmonary tuberculosis. In these observations and others previous to the studies of Sabin and her co-workers (1923–1925) and of Medlar (1926–1929) the monocytes and lymphocytes,—important features in the cytology of tuberculosis,—apparently were not differentiated.

In the present study the blood counts were carried out in the following manner: The blood was drawn in the morning between the hours of ten and twelve, obviating diurnal variations. The leucocyte counts were made by one person. Wilson's stain was used to differentiate the leucocytes. Two hundred cells were counted. The following criteria were employed to distinguish the monocyte from the large lymphocyte: The monocyte is a large cell containing either a round or kidney-shaped purplish nucleus. Its cytoplasm stains a grayish-blue. The whole cell appears dusted over with fine purplish granules. The lymphocyte is a smaller cell containing an intensely stained and sharply outlined purplish nucleus. Its cytoplasm is a clear sky-blue color.

A series of blood counts, made on 31 healthy individuals between the ages of 18 and 47 years, was used as a standard. The total counts in this control series ranged from 5,000 to 12,000 and the differential counts showed striking variations, notably in the percentages of the lymphocytes and monocytes. The lymphocytes ranged from 15 to 47 per cent and the monocytes from 4 to 12 per cent. The average percentage of lymphocytes was approximately 7 per cent higher than that noted by other investigators,—a point to be considered in appraising the results. No adequate explanation was found for this discrepancy. Table 1 contains the average total and differential counts in the control group.

[1] From the New York State Hospital for Incipient Tuberculosis, Ray Brook, New York.

Blood counts were made on 76 individuals formerly treated at Ray Brook for moderately advanced or advanced pulmonary tuberculosis. All had had tubercle bacilli in their sputum on numerous occasions. At the time the leucocytic counts were made the individuals in this series had performed full-time work for periods ranging from four to twenty-five years. Table 2 gives the average total and differential counts; table 3, the individual counts in the 76 cases. The blood counts in this

TABLE 1

The average total and differential counts in 31 healthy individuals

Total white blood cells	7,800
Polynuclears	58.7%
Lymphocytes	32.3%
Monocytes	6.5%
Eosinophiles	2.5%
Ratio: $\frac{\text{Lymphocytes}}{\text{Monocytes}}$	4.9 to 1

TABLE 2

The average total and differential counts in 76 individuals with apparently cured pulmonary tuberculosis

Total white blood cells	7,050
Polynuclears	57.8%
Lymphocytes	33.6%
Monocytes	6.4%
Eosinophiles	2.2%
Ratio: $\frac{\text{Lymphocytes}}{\text{Monocytes}}$	5.2 to 1

group and the control group are practically identical, indicating that there is no residual change in the leucocytes in apparently cured pulmonary tuberculosis.

The following three cases are representative:

Case I

The X-ray films of J. M., who entered Ray Brook in 1921, revealed evidence of moderately advanced pulmonary tuberculosis with an antrum in the right lung (figure I). One year after admission he left greatly improved. He con-

TABLE 3

Total and differential leucocyte counts in 76 patients with apparently cured pulmonary tuberculosis

YEARS*	W.B.C.	POLY.	LYM.	MONO.	EOSIN.	RATIO
25	6,550	54	40	6	0	6.6
25	8,600	44	42	5	9	8.4
25	5,800	59	36	4	0	9
23	7,850	62	30	4	4	7.5
23	8,350	62	27	3	8	9
22	7,950	57	36	6	1	6
22	7,100	56	36	6	2	6
21	8,950	58	34	6	2	5.6
20	6,200	43	41	12	3	3.4
20	4,900	60	29	8	3	3.6
20	5,450	47	40	7	6	5.7
18	5,250	49	41	6	4	6.7
17	7,250	62	32	5	1	6.4
17	8,850	70	24.5	4.5	1	5.4
15	6,200	52	40	8	0	5
15	7,400	44	45	4	0	11.2
14	6,400	65	28	6	1	4.6
13	6,100	63	31	8	2	3.8
13	8,350	78	14	7	1	2
12	6,050	56	33	5	2	6.6
12	6,000	66	24	8	1	3
12	5,400	54	34	10	2	3.4
12	5,500	60	33.5	5.5	1	6.1
11	6,800	43	46	9	2	5.1
11	5,400	66	29	4	1	7.2
11	7,700	58	35	5	2	7
11	8,450	65	24.5	8	2.5	3.6
10	7,050	67	26	5	1	5.2
10	7,200	40	44	11	5	4
10	8,000	54	34	8	4	4.2
10	7,300	47	39	13	1	3.2
10	6,250	50	38	6	6	6.3
9	6,950	66.5	26	5.5	2	4.7
9	5,750	60	32	7	1	4.5
8	5,600	61	31	4	4	7.7
8	6,100	62	33	4	1	8.2
7	5,400	56	36	6	2	6
7	5,200	65	25	5	5	5
7	6,600	60.5	32.5	5	2	6.5
7	6,050	56	35	7	2	5
7	6,750	62	30	8	0	3.7
7	7,800	56	38	4	2	9.5
7	6,400	53	44	3	0	14.6
6	7,650	60	30	9	1	3.3
6	5,600	53	35	10	2	3.5

TABLE 3—*Concluded*

YEARS*	W.B.C.	POLY.	LYM.	MONO.	EOSIN.	RATIO
6	6,950	67	26	6	1	4.3
6	4,200	61	33	4	2	8.2
6	8,850	59	34	6	1	5.8
6	7,200	56	32	7	5	4.5
6	8,700	47	49	3	1	16.3
6	8,700	58	34	8	0	4.2
5	7,850	75	20	4	1	5
5	5,450	52	38	10	0	3.8
5	5,650	56	34	8	2	4.2
5	8,550	50	39	11	0	3.5
5	7,150	54	38	7	1	5.4
5	6,150	60	32	5.5	2.5	5.8
5	12,200	53	40	5	2	8
5	5,600	55	37	7	1	5.2
5	9,500	75	16	6	3	2.6
4	6,250	55.5	34.5	9	1	3.8
4	7,200	54	37	4	5	9.2
4	5,400	52	38	3	7	12.6
4	9,750	54	40	5	1	8
4	6,100	65	29	4	2	7.2
4	8,600	67.5	28	3.5	0	8
4	7,850	53	38	7	2	5.2
4	7,700	52	42	5	1	8.5
4	7,850	59	31	9	1	3.4
4	6,950	57	30	10	3	3
4	8,250	59	33	6	2	5.5
4	8,900	69	20	6	4	3.3
4	6,550	58	36.5	4	1.5	9.1
4	9,300	53	39	6	2	6.5
4	7,850	59.5	33.5	6.5	0.5	5.1
4	6,450	60.5	28	7.5	4	3.7

* Number of years since discharge.

tinued treatment for another year. After working 7 years as a clerk he returned for an examination. Films made at this time contained only a few discrete shadows indicative of calcified lesions (figure II). The blood picture was:

Total leucocytes..... 5,600

Polynuclears..... 53%
Lymphocytes..... 35%
Monocytes..... 10%
Eosinophiles..... 2%

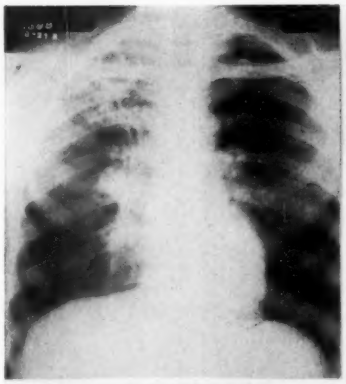


Fig I CASE I. Fig II

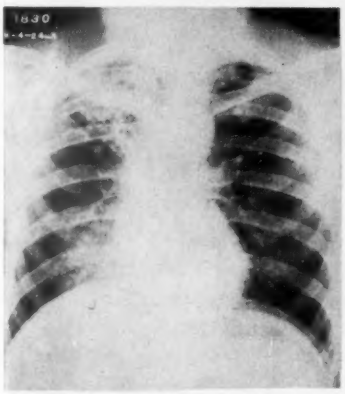
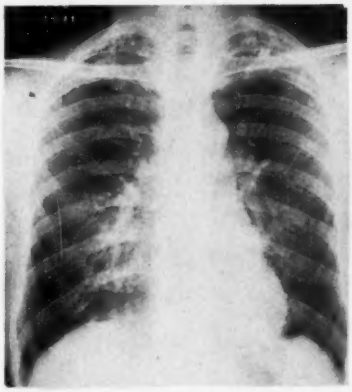


Fig I CASE II Fig II



CASE III Fig I

Case II

M. K. entered the hospital in 1924 with extensive disease of the lungs (figure I). His symptoms were of moderate severity and he was confined to bed during his stay, approximately one year, at the sanatorium. He continued treatment for two and one-half years; then began work as a salesman and has been employed in this capacity ever since. An X-ray picture made in 1931 failed to show any signs of cavity. The discrete shadows in the lung fields suggested healing by calcification (figure II). His blood count at this time was:

Total leucocytes	8,700
Polynuclears	47%
Lymphocytes	49%
Monocytes	3%
Eosinophiles	1%

Case III

C. B. entered the sanatorium in 1917, presenting evidence by physical and roentgenological examination of moderately advanced bilateral pulmonary tuberculosis. The patient was discharged after one year greatly improved. Subsequently he worked steadily as a salesman for 13 years and was then examined at Ray Brook. He was without symptoms and appeared to be in good health. On physical examination there were latent râles throughout both lungs. Stereoscopic chest roentgenograms showed that all the shadows had disappeared except some discrete ones confined to the summits of both lung fields (figure I). The blood picture was as follows:

Total leucocytes	8,350
Polynuclears	78%
Lymphocytes	14%
Monocytes	7%
Eosinophiles	1%

SUMMARY

1. In this study the average total and differential counts in persons with clinically healed pulmonary tuberculosis are essentially the same as those in healthy individuals.

2. With a few exceptions, the variations in the percentages of lymphocytes in the two groups are comparable.

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THE INFLUENCE OF PREGNANCY ON PULMONARY TUBERCULOSIS[1]

GEORGE G. ORNSTEIN AND MAURICE KOVNAT

In reading through the medical literature one cannot but have a pessimistic viewpoint regarding the influence of pregnancy on pulmonary tuberculosis. A large group of investigators, from Ortega (1) to the present, have added their evidence that pregnancy has a deleterious influence on the course of pulmonary tuberculosis. The figures vary, but, on the whole, report that over 50 per cent of the cases do poorly and go on to a fatal ending. Kaminer (2) reports bad results in 50 per cent of his cases; Merletti (3) also quotes 50 per cent; Lempert (4) 75 per cent; Von Rosthorn (5) 70 per cent; Von Bardeleben (6) 71 per cent; Pankow and Kupferle (7) 94 per cent; Reiche (8) 77 per cent; Schauta (9) 68 per cent; Parry (10) 50 per cent; and Bacon (11) 33 per cent deaths of cases in the first year.

A study of the cases at Sea View Hospital at first gave a similar point of view; but, on further investigation, it appeared that a pregnancy had very little effect on the course of the disease. The character of the pulmonary form of tuberculosis determined the destiny of the patient.

The records of the patients delivered at Sea View Hospital for the past ten years were studied. There were 85 cases in all. The average duration of stay before confinement was 2.1 months; and the average after delivery was 3 months. Through the courtesy of the Department of Health a follow-up of these cases was made possible. Unfortunately, due to falsification of names in municipal hospitals, and the frequent moving of people in New York City, a number of patients could not be found. In a larger percentage of cases they could be traced from one to five years.

Of the 85 cases, 31, or 36 per cent, died; 15, or 18 per cent, were unimproved and progressed; and 39, or 46 per cent, improved. Therefore, at first glance 54 per cent of our cases died or did poorly. These figures fit in with the statistics of the investigators quoted previously.

[1] From the Sea View Hospital, New York City.

Comparing these figures with a large group of females with tuberculosis uncomplicated by pregnancy at Sea View Hospital, 1,805, or 33 per cent, died; 1,696, or 31 per cent, were unimproved; and 1,969, or 36 per cent, improved. In this group of nonpregnant females 64 per cent either died or had a progression of their disease.

The question immediately arises as to whether it is fair to compare 85 cases as against 5,470 cases. We believe our percentages would probably be changed to only a small extent.

Bridgman and Norwood (12) reported the following: They compared 72 cases of uncomplicated tuberculosis in females with 20 pregnant ones. The figures of the uncomplicated cases are as follows: Died in first year, 32 per cent; worse 33 per cent; improved 35 per cent. In other words, 65 per cent died or progressed. These figures compare favorably with the above 5,470 cases. They report 20 cases of pregnancy and pulmonary tuberculosis, of which 50 per cent died, 40 per cent were unimproved and 10 per cent improved. Their figures are high compared with ours, but probably would have changed had their cases been more numerous.

Comparing the figures of pregnant with nonpregnant females with pulmonary tuberculosis it appears that the pregnant woman stands as good a chance as her nonpregnant sister, if not a better one.

We went a step further and investigated the character of the pulmonary pathological processes in our group of cases. The cases were classified according to the recent qualitative classification of Ornstein, Ulmar and Dittler (13). This classification, in addition to the "yardstick," is a qualitative classification. It divides pulmonary tuberculosis into two main groups: (1) exudative and (2) productive.

THE EXUDATIVE REACTIONS

The exudative reactions are characterized by high tissue sensitivity to tuberculous antigen, so that there is an immediate and explosive reaction whenever the tissue of the host comes in contact with tubercle bacilli. The extent of the cell irritation that occurs will be dependent upon the mass or concentration of the irritant bacilli; the greater the mass or dosage, the more likely the opportunity for overirritation and resultant cell death. On the basis of these reactions the exudative form of tuberculosis may be divided into two main types, namely, a type that grossly resolves and a type that does not resolve but rather leads to lung destruction. The resolving type is separated into two clinical

entities,—a very rapidly clearing benign exudative form, and a slower resolving exudative-productive form. The nonresolving type is termed caseous-pneumonic tuberculosis.

Resolving Exudative Tuberculosis

The Benign Exudative

Because of great tissue sensitivity, contact with a small amount of tubercle bacilli produces an exudative form of reaction. The response is chiefly serous, with little fibrin and a small amount of cellular element. There is little or no resulting death of tissue. The exudate is absorbed and the patient becomes well in a short time without leaving in the roentgenogram any visible trace of the previous infection.

The Exudative—Productive

With similar high tissue sensitivity but a larger dose of tubercle bacilli the reaction is more violent. Besides the serous exudate there is more fibrin and a great deal of cellular element. Fortunately, there is comparatively little resulting death of tissue. The exudate is again absorbed. After a longer time the patient becomes well again. Serial X-rays show a complete resolution of the exudate except for a few small areas of productive changes and an occasional fibrotic strand.

Nonresolving Exudative Tuberculosis

Caseous-Pneumonic Tuberculosis

Here, in addition to high tissue sensitivity, there enter large doses of tubercle bacilli. The reaction is severe with resulting death of tissue. There are caseation and necrosis. Following liquefaction of the whole mass the dead tissue is sloughed out, with resulting cavity-formation that characterizes this form of tuberculosis. From the walls of these cavities tubercle bacilli are constantly shed and become sources of superinfection. These patients are a constant threat to themselves, their families and their associates. They swallow large numbers of tubercle bacilli so that tuberculosis of the intestinal tract and the larynx is a frequent complication. To this form of pulmonary tuberculosis the term "malignant" has been applied.

The Productive Form of Tuberculosis

When tissue sensitivity is low and dosage of tubercle bacilli is small, the response is productive rather than exudative. The infection begins

in the terminal bronchiole and invades the surrounding mucous membrane. As a result of this infection there follows an obliteration of the bronchus with atelectasis of the terminal portion of the lung. The alveoli then becomes involved. The reaction is cellular. There is typical tubercle-formation with epithelioid and giant cells and fibroid changes. Aschoff (14) called this form of tuberculosis *acinous productive tuberculosis*. Because of avascularity, the lesions may break down and ulcerate into the smaller bronchi. Tubercle bacilli are then aspirated into adjacent portions of the lung. Infection now takes place through the small bronchi, the process slowly "browsing" down through the lung. Frequently the opposite lung becomes involved. The process begins in the apex and slowly descends. When extensive it may have the appearance of a blood-stream infection. This form of pulmonary tuberculosis has been termed "chronic-productive tuberculosis." The course is usually very slowly progressive. It most frequently manifests itself in the advanced stages. This productive form of tuberculosis takes about twenty years to involve both lungs.

In regrouping our pregnancy cases under this classification we had 51 in the caseous-pneumonic group, nine in the resolving exudative group, and twenty-five in the productive group.

THE CASEOUS-PNEUMONIC GROUP

There were 31 deaths, and they all occurred in this group of 51 cases. Of the remaining 20, ten left the hospital clinically unimproved, and ten clinically improved.

In this type of pulmonary tuberculosis following caseation there is cavity-formation, with thoracic deformity and displacement of the mediastinum and the trachea. Tubercle bacilli are constantly being shed from the wall of the cavity and opportunities for superinfection are always present. The toll in this type of pulmonary tuberculosis is very great. Barnes and Barnes (15) reported the fate of pulmonary tuberculosis in 1,454 cases with cavity as follows: 80 per cent died within one year; 82 per cent within 2 years; 85 per cent within 3 years; 90 per cent within 5 years; and 95 per cent within 15 years.

Accordingly, the prognosis in caseous-pneumonic tuberculosis is bad. The majority of cases end fatally. We must now consider, when this form of pulmonary tuberculosis is complicated by pregnancy, whether the great toll in human life is caused by the complication or the disease itself. We therefore compared 51 nonpregnant females having caseous-pneumonic tuberculosis with the pregnant group. In the pregnant

group there were 31 deaths (60.77 per cent); ten unimproved with progressive disease (19.6 per cent); and ten improved (19.6 per cent). In this group 41 cases (80.37 per cent) died or progressed, and ten improved (19.6 per cent). In the nonpregnant females there were 23 deaths in 51 cases (45 per cent). Twenty-five progressed (49 per cent) and three improved (6 per cent). In the nonpregnant group 48 cases died or progressed (94 per cent), and 7 cases improved (6 per cent).

In a follow-up of the discharged cases, unimproved and improved in the pregnant group, two of the unimproved and four of the improved group died. The toll of deaths in 51 cases was 35 in all, or 69 per cent in the first year. These figures are almost identical with a group of 700 cases of caseous-penumonic tuberculosis studied at the Metropolitan Hospital. The death-rate was 68 per cent in the first year.

RESOLVING EXUDATIVE TUBERCULOSIS

This is an acute form of pulmonary tuberculosis. The extent of the lesions varies from a lobule to a whole lobe. The reaction is chiefly serous with fibrin and cellular elements. There is little or no death of tissues. Resolution may therefore occur without leaving a trace or with a few fibrotic strands as evidence of previous infection. In the benign exudative group resolution may occur from six weeks to six months. In the exudative-productive form, because of more fibrin and cellular deposits, resolution takes a longer time.

There were 9 such cases. There were no deaths in this group. Seven of the cases were discharged from the hospital improved. Two were discharged as unimproved. In a follow-up of these cases three could not be traced, two of which were in the improved and one in the unimproved group on discharge. Of the remaining 6 cases there were no deaths. Two are in good condition one year after discharge. One is working and well five years after discharge. Two had been discharged from the files of the Department of Health as arrested cases the same year they were discharged from Sea View Hospital. One was well for two years and then could not be traced.

THE CHRONIC PRODUCTIVE TYPE

This type is the acinous-nodose form of tuberculosis described by Aschoff (16). The reaction is cellular productive and acinous in distribution. The process begins in the apex and slowly spreads through the lungs. There are few symptoms of toxaemia, and in the early and

the minimal stages the tuberculosis is rarely discovered. The prognosis is usually good in this form of tuberculosis, most of the cases dying late in life.

There were 25 of these cases. No deaths occurred during their stay in the hospital. Twenty-three were discharged as improved and two as unimproved.

Going through the death-files in the Department of Health, there were only two deaths in the whole group since 1921. We were able to trace fourteen of these cases. One must constantly keep in mind that fictitious names are frequently given in municipal hospitals. Of the two deaths both had extensive bilateral chronic productive tuberculosis. Both died one year after delivery. One had been discharged as unimproved (progressive disease) and the other as improved. Of the remaining 12 cases, seven had been discharged from the files of the Department of Health as arrested. Of these 7 cases, one was discharged the same year, two were discharged as arrested twelve months after leaving the hospital, two patients two years after leaving the hospital, one patient three years after leaving the hospital, and one three and a half years after leaving the hospital.

Of the remaining 5 cases one was discharged from the hospital as unimproved and is still alive after five years; she is at home and goes to the clinic for check-up and treatment. Another is at home five years after delivery but not discharged as arrested. One was well for one year after delivery but was lost trace of in 1926. One is at home one year after delivery and remains well. The last case discharged from the hospital as improved on October 14, 1931, has returned to the hospital seven months pregnant and is in excellent condition.

Pregnancy has very little influence on the course of this form of pulmonary tuberculosis.

SUMMARY

Upon first glance at a group of cases of pulmonary tuberculosis complicated by pregnancy, one cannot help forming the opinion that pregnancy has a deleterious effect on the disease. We have already quoted investigators formulating such an opinion. In reviewing the series of cases at Sea View Hospital we first came to the same conclusion. When we compared the series with a group of nonpregnant females we were surprised to find that the death-rate was almost the same as in the nonpregnant group. Apparently the pregnant female has as good a chance

for recovery as has her nonpregnant sister. We come back, therefore, to opinions expressed at the beginning of this paper.

Other investigators found similar results. Marshall (17) and his associates compared a group of pregnant and nonpregnant cases of pulmonary tuberculosis. There were 309 nonpregnant and 203 pregnant females in various stages of the disease. In his group called "dormant" or "healed" pulmonary tuberculosis 2 per cent of the nonpregnant and 1 per cent of the pregnant cases died the first year. In the advanced stages of the disease 46 per cent of the nonpregnant females died, compared with 37 per cent of the pregnant group. In Marshall's series the pregnant female had a better chance of survival.

Barnes and Barnes (18) had a similar optimistic report. They reported that the relative frequency of improvement in the positive- and negative-sputum cases corresponded closely with that of the nonpregnant group. They further reported that, of the 56 ex-patients of the Rhode Island State Sanatorium with positive sputum who are known to have had children during or since sanatorium residence, 31 per cent were living, while of all tuberculosis ex-patients only 26 per cent were alive.

In the series at Sea View Hospital the death-rate compared with the whole nonpregnant female group was slightly increased. The pregnant group had a death-rate of 36 per cent in contrast with 33 per cent of the nonpregnant group. Whereas the death-rate was slightly increased, there was a marked difference in the unimproved group. Here the pregnant females showed 18 per cent unimproved compared with 31 per cent in the nonpregnant group. This wide difference in a follow-up after sanatorium residence would greatly increase the death-rate in our nonpregnant group and our figures might be a good deal like those of the above-named investigators.

The next step naturally was a study of the cases. We soon found out why one case did well and another progressed to a fatal ending. At Sea View Hospital the "yardstick" classification has been abandoned as the sole method of classification of pulmonary tuberculosis. To it has been added a qualitative one which has been briefly described. We were pleased to find another investigator that felt the same about the uselessness of a quantitative classification. Pankow (19) stated that the previous indications in pregnancy and pulmonary tuberculosis must be rewritten because the old classification of tuberculosis was a localizing and a quantitative classification and not a qualitative one. He then

presents a favorable and an unfavorable qualitative classification with indications for each group.

We quickly found that the bad prognosis did not depend on the pregnancy but on the character of the pulmonary tuberculosis. All our deaths in the pregnant group at Sea View Hospital were in the caseous-pneumonic group. On the other hand, in the resolving exudative and chronic productive groups in which the prognosis is better and usually good, there were no deaths. In 34 such cases there were no deaths in the hospital and most all of them were discharged as improved. Pregnancy had only a minor effect on the prognosis of the disease in the caseous-pneumonic group, for which it shortened the usual span of life compared with nonpregnant group. In the other two groups there were no deleterious effects of pregnancy on the disease.

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THE PSYCHIC ELEMENT IN THE AETIOLOGY OF TUBERCULOSIS

MILES J. BREUER[1]

By way of introduction to a few case-reports and a statistical study, it would be appropriate to define the position of psychic causative factors in the general scheme of tuberculous aetiology.

All disease is the failure, to a greater or less degree, of adaptation between the living organism and its environment. Only such forms carry out their organic cycle successfully as are in equilibrium with the environment in which they exist. Any intolerable disturbance of this equilibrium results in injury to structure or function, the intensity of which may vary from a degree which has little, if any, significance, to actual death.

For example, in the case of the amoeba, the drying and cooling of the environment causes a slowing-down of pseudopodic and granular motion, if gradual encystment may ensue; and, if too rapid and intense, death results. In the human being, injury in an automobile wreck, colic from the eating of green apples, inflammation from bacterial infection, or mental disease from parental mishandling or insoluble emotional problems, are disturbances of the adaptation of the individual to his environment.

Among animal species, man has survived so long and progressed so far because he adapts most readily to the widest range of variation in environment. With few exceptions, he has become adapted to living in all corners of the earth under the conditions found there, of climate, temperature, moisture, altitude, pressure, solitude, crowding, noise, etc. He survives the variation in environment and eventually comes to an equilibrium with it. No other species has withstood anything approaching such a variety of environments.

Environment may be natural or man-made. During a very recent period of his existence on earth, man has created an entirely new environment for himself. He has become civilized; and lives in houses and

[1]Lincoln, Nebraska.

cities, artificially heated, and enclosed from the circulation of the outer air. This living in houses and cities, as an environment, has carried with it, inseparably, the tubercle bacillus. The tubercle bacillus is part of man's environment since civilization has stepped upon the scene, and it must be taken into consideration whenever environment is discussed in past and present civilized history.

Although the tubercle bacillus has appeared only very recently indeed in man's environment, nevertheless the human body possesses a fairly adequate mechanism for adapting itself to it. This is not the place to discuss the origin of that mechanism, except in so far as to say that it consists of no new elements appearing in the human organism since civilization has begun; but that it is put together from components that have existed in the animal body from the most primitive forms,—the foreign-body reaction, and the allergic reaction to foreign proteins, and the processes of inflammation and repair. Consequently, we find that the human race survives under the environment of house and city dwelling created by civilization, although it has had to modify bodily function and structure to make the adaptation.

That is: the contacts made by the individual with the factor of the tubercle bacillus in his environment, and the reactions thereby produced, build up a resistance within him, which preserves him as a functioning unit in his social group, except in such cases in which the process of adaptation has failed to reach the usual equilibrium. From the standpoint of the pathogenesis of tuberculosis, the individual's whole life is merely a story of the effort to build up and maintain a resistance to tuberculosis. The great majority of us do this successfully, and survive. When there is a defect in the building-up of resistance or in its maintenance, the individual becomes diseased, and eventually succumbs.

Disturbances in this adaptive process may be purely environmental in cause, such as the accidental coming in contact with massive infection; or they may be lowerings of the resistance against tuberculosis by a failure of the individual's part to carry out such living habits as are necessary to maintain this resistance. Overfatigue, faulty diet, and lack of sufficient contact with outdoor sun and air are commonly known factors, supposedly under the individual's control, which will lower resistance, and permit the development of tuberculous disease.

The most important adaptive mechanism in the human body is what we are accustomed to call "the mind." Despite numerous other uses to

which we are trying to put it, the human mind is nothing more or less than an organ to assist the material body in adapting itself to its material environment. The entire history of the development of the human mind exhibits, running parallel to it and its results, more comfort, better living, and greater safety for the human race.

Mind serves this adaptive function by coördinating bodily functions, past experience, and the perception of the external environment, into a single field, which we call *consciousness*. At the various levels of this field, the necessary requirements for successful behavior can be tested and planned, before any bodily activity occurs. In a species not possessed of mind, Nature sacrifices a million individuals to a biological experiment. In a species gifted with mind, it is possible to test out a million possibilities of action without the loss of a single individual to the race. The conscious mind means to the body what the research laboratory means to the industrial plant.

In maintaining adaptation to tuberculosis in the environment, the mind calls forth such behavior in the body as will produce and maintain resistance. In the more primitive stages, mental activity was on lower levels, popularly called "instinctive." Men got food, air, sun, rest, and activity, and avoided the presence of heavily infected persons, with much less conscious registration of their efforts than we do. We civilized people carry in our consciousness a picture of the possible dire results that may occur to us if we do not carry out proper habits of living; we carry them out by close attention, instead of by impulse. There is not much essential difference between the two methods; what difference there is, is quantitative, and the latter method is the more efficient.

It seems a simple statement to make, that the mind looks after the interests of the body and keeps it protected against tuberculosis. As a matter of fact this process is delicately balanced and easily upset. At the present day it is upset very frequently indeed by factors which civilization has created for us, and against which our bodily organization possesses no protective mechanism: that is, by the psychic stresses of modern life. Many of the difficult behavior problems of modern civilized life are so new in the history of the race, that their effects are those of a sudden shock. Only the conscious, logical, reasoning mind knows how to attempt to deal with them; all the lower levels of our living are totally unprovided with protective or defensive means.

We are familiar enough with severe cases of neurosis or psychosis, in which the patient refuses to move or eat. The functions of the mind

have broken down, and those of the body have followed them in a heap of wreckage; death of the individual results except for the help of other individuals. Such cases are extreme examples. Milder degrees of disturbances of the coördinating functions of the mind produce physical changes that are slighter or slower in evolution, and less readily noticeable to the untrained observer, but they are none the less certain. It has become an axiom that physical deterioration surely follows as soon as the mind ceases functioning at its best. In such mild cases, behavior changes may be almost unnoticeable, in contrast to the severe types mentioned at the head of this paragraph; their consequences can always be found eventually. When the mind ceases to care, the body suffers.

The mental elements that go to make up a behavior necessary to maintain resistance against tuberculosis are subtle, and difficult to put one's finger on:—that interest in life that maintains vitality, that poise and peace required for proper nutrition, the impulsive desire for food, relaxation, exercise, and the out of doors,—such as are part of a normal mental equipment. It takes a thoroughly wholesome bringing-up and a well-balanced life to form and maintain these habits properly. Maladjustments in the work-life, the social life, and the emotional life easily produce upsets which undermine the resistance-maintaining way of living. Therefore, it is not surprising that psychic disturbances, such as long-continued mental conflict, excessive fatigue, or emotional situations from which there is no escape, result in tuberculosis.

The records of the last hundred consecutive cases of tuberculosis coming into my office have been examined in the effort to learn as much as possible about such relationships. These cases cover a period during which my attention has been focused on the psychic element while I was studying and treating the patient.

1: No psychic factor in the aetiology.....63 cases
Of these 63, those giving insufficient opportunity for study to exclude psychic factors..... 3
2: Marked neurosis secondary to the tuberculosis..... 3
3: Psychological factor in the aetiology..... 34
4: Types of tuberculosis among psychic cases
Exudative or caseo-necrotic..... 5
Proliferative or fibrous..... 29
5: Types of tuberculosis among nonpsychic cases
Exudative or caseo-necrotic..... 2
Proliferative or fibrous..... 58

6: Types of psychic disturbance

Neuroses

Parental mishandling in early life	8
Marital difficulties	11
Constitutional difficulties	9
Occupational maladjustment	3
Psychoses	4

The fact that, in 34 per cent of this series, psychic factors contributed to the causation of tuberculous disease, suggests that modern life has other methods of producing tuberculosis in addition to crowding, lack of air, sun, and proper food. The high-pressure mental pace at which we travel is at present a nonadjusted state, and tuberculosis is one of its penalties.

Eighty of these cases were studied thoroughly enough and over a sufficiently long period of time either to make a diagnosis of the psychic factor, or to exclude it definitely. The other twenty disappeared from observation, and all that can be said about them is that the mental reactions were not apparent after seeing the individual a few times and making a physical examination.

The neurosis mentioned as being secondary to the tuberculosis will not be discussed here further than to say that it is the well-known anxiety state caused in susceptible individuals by the prolonged period of concern over life and health and close attention to every detail of personal behavior.

It will be noted that there is a much higher proportion of severe, progressive tuberculosis among those with a psychic factor included in their aetiology than in the others. In the nonpsychic type, 2 cases out of 60 makes 3.3 per cent. In the type burdened with emotional problems, the proportion of progressive cases with poor prognosis is 5 out of 29, or 17 per cent. If conclusions may be drawn from this small series it suggests that the general observations as to the importance of psychic balance to bodily recovery are confirmed.

To illustrate types of psychic disturbance, cases will be briefly cited:

1: Female; age 24; severe proliferative lesions in both lungs. The patient was raised by markedly mismated parents and conflict reigned. There were expectations of wealth to be inherited, and she was brought up to act the part of a wealthy lady. The wealth was swept away before its possessor died; as a result of the depression the father finds making a living difficult and the family lives almost in poverty. The patient is unable to work, both because

of her tuberculosis and because of her attitude toward life that she ought to have been wealthy and isn't. Raised in a harmonious home and taught how to adjust properly to life in her social group, she would now be well and making a living, instead of presenting an almost hopeless problem. The tuberculosis is her escape from a problem that has no other solution for her.

2: Female; age 32; large exudative area in the left apex, possible cavity. Two children, 9 and 11 years of age. Her husband is an insurance inspector and travels considerably. For a number of years she has been finding letters in his pockets from a woman in another city, and poetry written by himself addressed to this woman. When faced with the findings, he read her some of the poetry and regaled her with accounts of the other woman's beauty and charm. Yet the patient does not wish to divorce him. Under hospital treatment, and then at a suitable occupation outside her home and away from him, she improved and will probably recover.

3: Male; age 28; married; no children. Raised in a Southern Illinois mining town. No ear-lobules; eyes widely spaced; upper incisors broad and wide apart. He is a violent communist, does not work, allows his wife to support him, and comes in for examination to see if he is fit to go on a hunger-march or some other demonstration. He has severe proliferative lesion in both apices. He is constitutionally maladapted.

4: Male; age 28; proliferative lesion marked in right apex, less so in left. Drove a laundry-truck to earn enough to take a year's work in business administration in the University; worked hard and studied late while in school; and grew worse during this period. Was advised to go back to his laundry-truck, where he improved. A careful history of his past indicates that he was always at his worst at indoor work, and always improved at light work out of doors. He must decide between a career as a rising business man with tuberculosis, or as a healthy truck-driver.

5: Male; age 32; single; farmer. Widespread proliferative lesions. Works a farm alone and lives on it alone. He brought in a sample of his sugar one day, into which he complained that a neighbor had put poison, which was producing his chest and epigastric pains. He states that his neighbors have done such things as setting fire to his straw-stack, shooting at him with a pistol at night, poisoning his pigs. His appearance is morose and depressed. He has been going along thus for many years, alone and just enough adjusted to make a living on his farm,—probably a low-grade dementia praecox. He will probably go on for many more years before he succumbs to his tuberculosis.

SUMMARY

1. The tubercle bacillus is a factor in the environment of civilized man.

2. The mind is a necessary part of the mechanism of adaptation for survival. Interference with the adaptive function of the mind results in disturbance of physical adaptation, and in tuberculous disease.

3. A hundred consecutive cases of tuberculosis are reviewed to illustrate this, and, as far as the series goes, confirm it.

GIANT SACCULAR BULLA OF THE LUNG

Report of a Case, with a Discussion of its Formation[1]

WEBB HAYMAKER AND A. A. KARAN

Bullae confined within the limits of the lung are of not uncommon occurrence; occasionally they attain large dimensions. A striking instance of such a bulla was reported by Miller (1) in the recent literature. Of more rare occurrence, however, are large bullae projecting beyond the normal contour of the lung. Porcher (2), in 1881, described a bulla, three by two inches in diameter, projecting two inches beyond the surface of the lung. He remarked that it was the largest he had seen during thirty years' autopsy experience in Charleston, South Carolina. However, from his fragmentary description, it is difficult to determine whether that specimen was a bulla or a bleb. It might be added that, despite the precise definitions given by Watson (3), in 1850, and by Miller (4) (5) in his recent histopathological studies of blebs and bullae, these terms have been incorrectly used as synonyms. The largest bulla we have been able to find described in the literature was in a report of Bouillaud's, cited by Watson (3). It had attained the size of a stomach of ordinary dimensions.

From the available literature, we could find no mention of the influence fibrous pleural bands play in the formation of blebs and bullae in emphysematous lungs. The following case exemplifies the mechanical effect of such fibrous adhesive bands upon forming blebs and bullae. Furthermore, this case illustrates the likely sequence of events taking place in the progressive enlargement of a bulla, attaining the dimensions of a giant sac which projected from the lung.

REPORT OF CASE

S. M., male, aged 49 years, was admitted to the Rhode Island State Sanatorium, August, 1933. Past history inconsequential. Onset of present illness was in March, 1931, with shortness of breath as the most prominent symptom; there were also productive cough, loss of weight and strength. The patient was treated for "asthma" until a chest roentgenogram and examination of the

[1] From the Department of Pathology, State Sanatorium, Wallum Lake, Rhode Island.

sputum disclosed the presence of pulmonary tuberculosis. He was then admitted to the State Sanatorium.

Physical examination of the chest revealed crepitant râles over the upper third of the right lung, posteriorly. Over the remainder of the lungs, there were sibilant and sonorous râles. Breath-sounds were suppressed over the region of the right middle and lower lobes. Pulse and temperature were normal. Tubercle bacilli were found in the sputum (Gaffky II).

Interpretation of a roentgenogram of the chest was that of a fibrotic type of tuberculosis in both upper lobes and a right-sided pneumothorax.

To alleviate the patient's increasing dyspnoea, a needle was inserted into the supposed right-sided pneumothorax and 800 cc. of air were removed. Temporarily, symptoms subsided. Twelve hours later, dyspnoea returned; and this time 2000 cc. of air were withdrawn. Again the patient was only temporarily relieved. On October 25, 1933, a cannula was inserted through the 6th right interspace in the anterior axillary line into the supposed pneumothorax cavity. Despite this procedure, dyspnoea continued. The patient's condition became progressively worse, with death occurring October 29, 1933.

(The clinical and roentgenological aspects of this case are being published in detail in another periodical (6).)

Postmortem Examination

Removal of the chest-plate exposed, on the right side, a large, pale, distended fibrous sac springing from the midportion of the lung in the midclavicular line, and extending downward to the diaphragm. The sac was intact except for a rounded laceration in its lower lateral wall (produced during life by insertion of a cannula). Compressing the lower lobe beneath it, and increasing in diameter as it proceeded downward, the sac spread out and became lightly adherent to the entire circumference of the pleural surfaces including the diaphragm.

With removal of the lungs, the relationship this saccular structure bore to the lung became more clear. The sac (figure 1), whose outer lining was directly continuous with the visceral pleura, took its origin abruptly from the upper border of the lower lobe by means of an air-containing pedicle 3 cm. in diameter. When spread out, the sac measured 18 cm. in length and 9 cm. in width and had a capacity of about 275 cc. of fluid (measured after formalin fixation).

Upon longitudinal section, this sac was identified as a bulla. It was completely air-containing and its wall measured between 2 and 3 mm. in thickness. The pulmonary border of the interior of the bulla consisted of a shallow, compressed parenchymal surface devoid of bronchiolar endings. The inner aspect of the bulla was lined, in its upper half, by somewhat emphysematous pul-

monary tissue directly continuous with the pulmonary parenchyma. In the lower half, however, parenchymal tissue became stringy and sparse. Vessels and bronchioles, found for the most part on the mediastinal aspect of the bulla, emerged from the upper half, to course down its interior, terminating

Fig. 1. Vertical anteroposterior section through right lung in the region of the midclavicular line. The uncut pedunculated bullous sac projects from the upper portion of the anterior surface of the lower lobe. A fibrous pleural band stretches from the lower border of the upper lobe to the uppermost portion of the bullous sac. A bleb protrudes from the lung a short distance below the lower boundary of the pedicle of the bulla.

as a tangled mass in its lowermost portion. The bronchus supplying the bulla was the first ventral branch below the hyparterial bronchus; it quickly divided into two branches which coursed down the wall in its mediastinal aspect. The bronchioles in the upper half of the bulla were patent; below that, they became

Fig. 2. Vertical lateral section through the anterior portion of the left lung. A fibrous pleural band, approximately in the midclavicular line, stretches between the upper and lower lobes. At each extremity of the band is an early bulla, the lower being the more recently formed.

too fine to dissect. Whether or not their naked ends were open was not determined.

Proceeding now to the gross description of the lungs proper (figures 1 & 2): The oldest lesions were the partly calcified caseofibrous nodules, 1 to 5 mm. in diameter, scattered through the upper lobes, the right middle lobe and the apices of the lower lobes. Adjacent to and surrounding these nodules were darkly pigmented areas of tuberculofibroid disease. The predominating lesion, however, was that of patchy interstitial and subpleural emphysema, which gave to the cut parenchymal surface a coarsely spongy, blanched appearance. The two upper lobes and the right middle lobe were markedly shrunken and covered with a thick fibrous pleura. There was a complete pleural symphysis over these lobes. The parenchyma of the two lower lobes was, for the most part, free from emphysema; the periphery, however, was the seat of a number of blebs and bullae.

It is of particular interest to describe in some detail the relationship fibrous bands bore to blebs and bullae. Beginning with the giant bulla, it was noted that from the under surface of the right upper lobe there stretched downward across the interlobar septum a single flat fibrous band (figure 1) which attached itself to the subjacent anterior surface of the lower lobe. The band measured 15 x 6 mm. It met the pleura of the lower lobe at the level of the uppermost portion of the pedicle of the giant bulla. The interlobar septum was elsewhere free from adhesions except for a frail one situated deeply in the interlobar fissure just lateral to the band described.

One bleb (figure 1), situated 2 cm. below the pedicle of the giant bulla, was 10 mm. in diameter. To its lower aspect was attached a short thick adhesion binding it to the subjacent diaphragmatic pleura.

In the contralateral lung, in the uppermost portion of the lower lobe in the mid-clavicular line, there was a pleural elevation (figure 2), 2 x 1 cm. in diameter, strongly suggestive of an early bulla. It differed from a bleb in that it did not possess a thin translucent mesothelial layer separated from its underlying parenchymal tissue. Over the upper portion of this bullous projection was attached a ribbon-like fibrous band, 12 x 5 mm. in size. The band stretched upward to find its origin in the lower border of the upper lobe. Its appearance and location were very much the same as that attached above the giant bulla on the contralateral side. The one striking difference was that the band on the left side was attached not to a stable pleura, but to the sagging wall of a distended pleura.

Microscopic Examination

A section taken through the upper portion of the giant bulla showed a hyalinized fibrous wall covered with a hyperplastic mesothelium. Within, the bulla was lined by sparsely distributed, distended alveoli, the trabeculae of

Fig. 3. Photomicrograph of section taken through the fibrous pleural band and the lower bulla pictured in fig. 2. At the upper part of the photograph is a fibrous pleural band attached to the upper portion of the lower lobe. The band is continuous with collagenous tissue extending downwards and ending about a tuberculous nodule. Partly surrounding the nodule is a bulla. The hyperplastic subpleural tissue adjacent to the band is the seat of haemorrhage. Hematoxylin-eosin stain. × approximately 20.

which were thickened by interstitial cell proliferation. The blood-vessels, including the alveolar capillaries, were distended; the walls of the former were the seat of rather extensive proliferative changes. The few bronchioles were found patent and their walls invaded by inflammatory cells, mainly polymorphonunclear leucocytes. Within the alveoli were scattered groups of pigment-containing macrophages. Study of a section in the lower portion of the bulla revealed similar pathological changes. Alveoli were, however, much more sparse, and vessels showed a more pronounced intimal thickening to the point of occlusion of their lumina. The bronchioles still remained patent.

Fig. 4. Photomicrograph of the pleural and subpleural tissue adjoining the lower end of the fibrous pleural band (see figure 3). It shows an extensive haemorrhage into the subpleural tissue. Haematoxylin-eosin stain. ×600.

Microscopic study of the left lung included a longitudinal section through the two bullae with their intervening fibrous band, described in the gross specimen. The section showed the fibrous band stretching from a conglomerate mass of caseofibrotic tubercles above, to another similar mass below. The lower bulla (figure 3) was centered about a tuberculous nodule and collagenous tissue, which were directly continuous with the interlobar fibrous band. The alveolar walls were separated from their previous attachments to the tuberculous lesion and were lying free in the bullous space as thickened alveolar walls. In the subpleural tissue continuous with the fibrous band,

there was a massive haemorrhage (figure 4). The alveoli adjacent to the bulla were for the most part small and thin-walled.

Briefly, the microscopic appearance of the aforementioned upper bulla in the left lung was that of rupture of most of the alveolar walls about the tuberculous prolongation of the fibrous band. The few remaining alveoli were thickened.

DISCUSSION

From the evidence presented, it is quite likely that fibrous adhesive pleural bands play an active rôle in the production of bullous sacs protruding beyond the limits of the lung. In the following discussion of the present case, the influence of such bands upon three bullae and one bleb will be considered; two instances, namely, the giant bulla and the bleb, represent the end-stage; the other two, both small bullae, are in all likelihood in the incipient stage.

At the uppermost aspect of the pedicle of the giant bulla there is attached a fibrous band held taut by the above adherent, and therefore stationary, middle and upper lobes. This band is adherent precisely at the point where the bulla originated. It is reasonable to assume that, in this area elective for emphysema, the fibrous band attached above that area exerted an additional strain upon the alveolar walls of the forming bulla. This strain was accentuated with each inspiratory movement which carried the lower lobe downward. The band being stationary above, because of total pleural symphysis about the two upper lobes, pulled with each inspiratory effort on the structures comprising the bulla beneath, particularly the tuberculous prolongations of the band, with rupture of more and more alveolar walls. With increased intra-alveolar pressure there was progressive bulging of the bulla, which developed into a protruding sac later burrowing downward to meet the diaphragm. With it, the sac carried down pulmonary parenchyma, which, in its present end-stage, lines the inner aspect of only the upper half. It carried, in addition, a lower-lobe bronchus and numerous blood-vessels which coursed to the bottom of the sac. At an earlier stage in the formation of the sac it was probably entirely lined with pulmonary parenchyma.

The distention of the sac to the proportions found at autopsy may be explained by an alteration in the inspiratory and expiratory exchange of air. Whereas the air could easily enter the sac through the distal

bronchial tree and surrounding sparse parenchyma, it could not easily escape. Thus there developed a progressive accumulation of gas in the sac.

The mechanical effect of the band-like adhesion attached to the bleb situated below the giant bulla is obviously a different one. Here, instead of straining the alveolar walls, the band, as it became older and contracted, pulled the wall of the bleb downward with it, thereby increasing its size considerably.

In the other two bullae, that is, those joined by a fibrous band, the upper is obviously the older, and it illustrates the effect again of the constant downward pulling force of a fibrous band. In the bulla beneath it, the influence of the band is quite different. This latter bulla, it is believed, is being formed in a manner analogous to the mechanism by which the giant bulla formed; namely, by a rupture of alveolar walls just beneath the point where the adhesion, identical in appearance to that of the giant bulla, was attached to the lung surface. The photomicrograph of the area (figure 3) shows how rupture has taken place immediately subjacent to the prolongation of the adhesion with accompanying burrowing of air deeper into the lung and up to its surface. Additional evidence of the strain exerted upon the lung by the band is the presence of recent haemorrhage into the subpleural tissue at and below the conjunction of the fibrous band with the pleura (figure 4). It is quite possible that in time a greater projection of this bulla above the pulmonary surface would have resulted.

SUMMARY

A rare case of a giant bulla projecting beyond the limits of the lung in the form of a sac is reported. It is part of the picture of compensatory emphysema complicating pulmonary tuberculofibroid disease. There is presumptive evidence that an interlobar fibrous pleural band was in a large measure instrumental in causing the bulla to attain such a large size. The mechanical effect of such a fibrous band on an early bulla in the contralateral lung is described in detail to illustrate the development which presumably took place in the incipient stage of the giant bulla.

The authors are grateful to Dr. R. P. Crank, Pathologist to the State Hospital for Mental Diseases, Howard, R. I., for his generosity in photographing the gross specimens and microscopic sections.

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Ray William Matson
1880-1934

Ray Matson died a tragic death. Perhaps it was fitting. Several centuries ago he would have been the beau ideal of Dumas's Musketeers. Graceful, handsome, well-groomed, ever alert and self-assured, exquisitely poised, and with a characteristic "swing" to his every movement, incisive and decisive, always up for adventure and a hazard, he indulged this sheer *joie de vivre* in fine horses and steeple-chasing and later in aeroplanes,—now, that modern convention had sheathed the sword.

Nevertheless, Ray died too soon. The Northwest realizes this; the West realizes it; and, in time, the medical profession of the country will realize it.

For one thing, he had that rarest of characteristics in this much-scrambled age,—a sense of perfection in every endeavor, not to mention the utmost thoroughness in everything that he did. At a time when average writers would send in reports of, say, a dozen cases of this or that, Ray would assemble a hundred, with every jot and tittle attended to. He honored the AMERICAN REVIEW OF TUBERCULOSIS with one important contribution after another; and the REVIEW will be the poorer for his passing; and so will be first-class clinical medicine.

This is not hyperbole. For, underneath, Ray was a thinker: he was even a moody man. No pertinent clinical observation escaped him. And, when he came to assemble the residua of a rich experience, he would labor long,—over the correct analysis, the proper expression, the right term,—when, then, entered the sense of perfection that would "paint the lily" of a job well-done.

Ray loved life, but he loved his profession better. None but his most intimate friends can know how he strove and strove to contribute to medical knowledge, to technique, to method. He played much, but he never had "medicine" out of his mind.

If he were not at his every-day practice in Portland, he was always abroad, observing and studying Continental practice,—usually in Vienna; and his keen mind seldom failed to observe and bring back to this country something that was of fundamental clinical value.

Ray had that other gift of the able and complete man—discrimination, whether of work or of men, and which, after all, means *taste*. He not only sought the best, but he followed it and moulded his own efforts along its lines. And it was this trait that contributed not a little to his remarkably successful career.

Berger Studio

Ray William Matson
1880-1934

Born in Brookville, Pennsylvania, on January 21, 1880, Ray Matson was graduated from the University of Oregon Medical School in 1902. He then spent three years as Resident Physician of the Good Samaritan Hospital, Portland, during which occurred one of his more exotic experi-

ences as Surgeon on the Steamship Lothian, engaged in transporting Chinese laborers from China to Mexico. From the beginning of his private practice in Portland, he specialized in tuberculosis, interspersing the routine of practice with frequent trips abroad: for instance, to Vienna in 1909, 1914, 1920 and 1925; University of London, 1909; University of Berlin, 1920; and University of Paris, 1919.

Interested in tuberculosis from the beginning of his medical career, he had, by 1920, become an international authority on the subject. His interest dealt chiefly with early diagnosis and collapse therapy, and in the latter when it was a virgin field in this country. He was the pioneer in oleothorax in the United States, and his contributions on this subject and on phrenic neurectomy have become classics in America. As a diversion, he also translated Wolff-Eisner's *Clinical Immunity and Sero-Diagnosis* from the German.

His war service was notable. Beginning as Major and President of the Examining Board at Vancouver Barracks in 1917, and devising a system for the elimination of tuberculous registrants from the army, he was sent over-seas as divisional gas officer, 91st division (Wild West), and participated in the battles of St. Mihiel, Meuse-Argonne and Ypres-Lys. Upon the cessation of hostilities he was appointed Lieutenant-Colonel in the Medical Reserve Corps.

Always broadly and deeply interested in local medical affairs, especially in public health, among Doctor Matson's more important interests and positions were city health-officer and city-physician of Portland (1906); associate medical director of the Portland Free Dispensary since its inception (1907); associate medical director of the Portland Open Air Sanatorium since 1916; member of the medical staffs of Multnomah County and Good Samaritan Hospitals; Professor of Histology, North Pacific Dental College (1905); Assistant Clinical Professor of Medicine, University of Oregon Medical School (1925–); and surgical consultant to the U. S. Veterans Administration Hospital (1930).

Although living at a great distance from the usual places of meeting, Doctor Matson was a frequent, if not indeed an assiduous, attendant at the annual meetings of the National Tuberculosis Association and the American Clinical and Climatological Association, of each of which he had been a Vice President. His other professional memberships included the American Association of Immunologists, American Association for Thoracic Surgery, International Pneumothorax Association, American Medical Association (fellow), Oregon State and Portland City and

County Medical Societies, Northwest Association for Internal Medicine, and the Pacific Interurban Clinical Club, and the Alpha Kappa Kappa and Alpha Omega Alpha medical fraternities. He had many times been a delegate to the *Union Internationale contre la Tuberculose*, and was, at the time of his death, President of the Portland Academy of Medicine.

Any mention of Ray Matson and his successful career could not be complete without reference to his wife, *nee* Carolyn Holmes. Privileged friends, permitted to share the open-hearted hospitality of the Matson home on Flanders Street, will always remember the gracious and attractive matron who presided over this tasteful and comfortable *ménage*. It was here that "Tat" Matson provided a recuperative refuge for a hard-working and hard-playing physician, and took no small part in stimulating him and keeping him fit for an ever-widening and more burdensome career. There are literally thousands who condole with her deeply.

Nor may one forget Ray's twin brother, Ralph. Between them they presented a model of team-work in practice and performance that was almost unique; so that at the peak of their maturity "Matson" had become a name to conjure with throughout the Far West, and, indeed, nationally and abroad. They had, in fact, established a "school" and a large and loyal "following." Few physicians west of the Rockies considered their beginnings or training in the surgical treatment of pulmonary diseases sound or complete until they had made the long journey to Portland,—to "watch" the Matsons and to work under them, and with that third talented member of a famous trio, Marr Bisaillon.

Ray's sudden death has been a crushing and well-nigh unendurable blow to his brother, Ralph, who has the heartfelt and inexpressible sympathy of the medical profession of the country. Yet, overwhelming as may seem the first emotional reactions to his tragic loss, it is this sympathy that will exert its steadying influence on a sorely bereft brother and nerve him on to a successful issue of what must appear an impossibly difficult task ahead. In this he has the fervent hopes and prayers of all of us.

A. K. K.

EDITORIAL

Pregnancy and Tuberculosis

The "literature" continues to yield its contributions to the perennial problem of the relation of pregnancy and tuberculosis. As usually posed, the question is: "Does pregnancy have an effect, deleterious or otherwise, upon tuberculosis in being, that is, concurrently present in the female body?" Concerning two such definite conditions as pregnancy and tuberculosis, so simple a question would seem capable of conclusive solution, yet present attempts to add to data and to swing or settle opinion indicate that the question is still *sub judice.* And this circumstance arouses the still more interesting question as to why uncertainty remains the result of many years of attention to the major problem. It may therefore be permitted one to indulge in certain reflections on why so unsatisfactory a situation obtains at this late date.

Merely a cursory examination of the customary treatise on the subject of tuberculosis and pregnancy is sufficient to suggest, if not prove the solution. Whether the individual inquiry approaches the problem biologically, statistically, clinically or, say, physiologically, it is at once apparent that, with few exceptions, the usual and average "study" proceeds from fallacious premises, gratuitous assumptions, and almost complete lack of definition and limitation of terms; and that from so unstable a foundation it limps through a morass of slip-shod data and the crudest handling of evidence to a palpably questionable conclusion.

For instance: far the greater number of papers carry in their titles the word "pregnancy," and it alone, in its relation to "tuberculosis;" and, in his first paragraph the author will state, as his purpose, the investigation of the effects of *pregnancy* on tuberculosis. Yet, before the alert reader has reached the third or fourth page he finds the author hopelessly mixing and combining three different and distinct maternal phases of the creation, early development and birth of every human being. Usually the author does not confine himself to pregnancy and its plain and probable influences on the mother. Only too often he lumps together pregnancy, parturition and the puerperium, and, in doing so, ascribes to *pregnancy* any and all influences that are alleged to exert an effect on the coexisting tuberculosis.

Now, pregnancy, parturition and the puerperium are, for a mother, completely separate events, consecutive yet sharply distinct and defined, and each with its own period of time. And it is not only conceivable, but probably true, that each individual phase can and does, on occasion, exert an effect on tuberculosis; in proof of which one need merely suggest what may be presumed to happen to a tuberculous woman by virtue of, let us say, an intoxication of pregnancy, or a complicated and stressful second stage of labor, or a puerperal infection. Certainly, it were anything but scientific to lay to *pregnancy*, in a woman who has tolerated her pregnancy extremely well, an activation or aggravation of her tuberculosis that has followed an abnormal, exhausting or dangerous second stage of labor (as has frequently happened). "Figures" derived from the laborious working over of hospital or dispensary records can be, and often are, positively misleading. How frequently are we presented with "figures" of women bearing children set off against "figures" of resulting or exacerbating tuberculosis in these same women, with the "controls" being either the "figures" of the terminal course of tuberculosis in nonpregnant or nonparous women or "figures" of the terminal course of parous or pregnant nontuberculous women! How often too are any differences of comparative "figures" ascribed to the effects of *pregnancy*! And how familiar are all of us with the lack or paucity of pertinent data included within average hospital records,—or with the "keenness" of detection of tuberculosis or even attention to it on the part of the ordinary specializing obstetrician,—or with the capacity of the tuberculosis specialist or of the statisticizing social worker or nonmedical assembler of statistics to recognize, weigh and interpret pertinent obstetrical data!

And, if figures ever lie, they lie the more loudly when they are gathered and presented "in the raw,"—with no allowances made for age, or for socioeconomic environment, or for primiparous as compared with multiparous women, etc., etc.

But, greater than any other fallacy in the customary approach to the problem of "pregnancy and tuberculosis" is the almost universal premise and assumption that pregnancy acts as a "constant" factor in whatever influence it may have on tuberculosis. That is to say, that all women tolerate pregnancy alike, which means nothing else than that the bodily economy of every woman reacts to pregnancy in the same way. Extensive reading would indicate that practically every author on the subject takes this most important datum for granted, notwithstanding its obvious falsity. Indeed, at the moment the writer cannot recall a

study of "tuberculosis and pregnancy," in which the author even casually suggested that pregnancy can act differently in different women or even differently in the same woman as one pregnancy follows another. Furthermore, although the assumption may not be stated, the writer gathers from not a few works on the subject that the authors labor under the impression that pregnancy is an evil experience, physiologically considered, for all women.

Nothing, of course, could be further from the truth. The most elementary practice soon teaches the observing physician that the bodily response of womankind to pregnancy is of almost "infinite variety." As a fundamental function of the female, pregnancy *as pregnancy* must be regarded as a normal function for the female; and, being so, it will, as does every other normal function, begin and proceed, with all due safeguards in being and at work, to the end that the integrity of the whole female organism be protected, and even improved. As the broader facts of pregnancy are disclosed to us, we learn for one thing that woman is most fertile during her earliest period of sexual maturity; and that the most fertile women throughout reproductive life are those who begin to bear children during their early years of maturity. We learn that after age twenty-five fertility falls off markedly and continuously until the end of reproductive life in those who have not borne children previously. We learn, moreover, that woman's fertility wanes in proportion as nervously she becomes more "sensitive" and more "highly organized," or, as some would have it, more "civilized" and "refined." Although we may now be entering controversial territory, there is a world of evidence to support the ages-old idea that woman's obstetrical troubles increase with her ascent in the socioeconomic scale, and its corollary that the more primitive woman bears her pregnancy, as well as labor, with the fewest difficulties: certainly the latter's puerperium is the easier.

In our society there are women for whom pregnancy is a positive physiological boon, and every succeeding pregnancy the more so. During every pregnancy their general well-being is sensibly and appreciably enhanced. Between pregnancies they retain their bettered health, and with fresh pregnancies go to higher levels.

There are other women for whom every pregnancy is an evil, physiologically speaking, and an unmitigatable evil. Their bodily economy simply will not tolerate pregnancy—to the point indeed that abortion must always be induced to save the woman's life. Such women, though capable of conception, and frequently so, are nevertheless actually sterile in practice.

And, as everyone knows, between the above two extremes there are women presenting every grade and degree of tolerance to pregnancy. There are what one may call "constitutional tolerance" to pregnancy and also "local tolerance," the latter conditioned by abnormalities, defects, infections, of the structures directly involved by pregnancy.

Such are the *facts* as concerns the effects of pregnancy upon woman, whether she be tuberculous or nontuberculous, or ostensibly healthy or diseased. And it would seem that any study or discussion concerning the influence of pregnancy on tuberculosis would have to take these facts into account. Indeed, to the writer, these facts must, of necessity, be regarded as the *primary facts*,—those which must form the basis of any inquiry of the kind under discussion. Even pseudoscience flies out the window when we are obliged to draw our conclusions from the data of ages lumped together, of nondiscrimination between the variables of reproductive history of women undergoing observation and study, and so forth. Any scientific treatise on the problem in general must take into account all factors mentioned above, as these are exactly determined.

Yet, after all, what are the ordinary clinical facts in regard to tuberculosis and pregnancy? Broadly they are that the association works both ways.

There are women whose concealed or mild tuberculosis is promptly and definitely activated or made worse by pregnancy, and often sensationally so. Such cases often stand out much more clearly in multipara than in primipara. For instance, and a concrete case: A gently bred woman, the wife of an obstetrician. Healthy before marriage and afterward, until her first pregnancy. Shortly after mid-term, pleurisy with effusion; to term, with birth of healthy baby, after which complete recovery from pleurisy. Healthy and normally active for several years. Both parents desiring another child, if possible, a consultation held between internist, tuberculosis specialist and husband of patient as to advisability of permitting a second pregnancy. Advice favorable. Occurrence of second pregnancy, with acute breakdown, tuberculous pneumonia, within a few months. Such cases are not rare; and in them a very careful history will disclose successive pregnancies marked by an increasing "show" of the symptomatology of tuberculosis, with remissions between pregnancies, until at last the volcano erupts—the case stands out, sharply revealed.

But there are also women in whom we observe the very opposite trend of events. This is best seen in actively tuberculous women who become

pregnant, or, less frequently, in whom tuberculosis is discovered at about mid-term or afterward—too late for an induced abortion on *general principles*. Many a time the physician, greatly concerned at first for the patient's welfare, will have the woman tell him that she has been feeling much better since pregnancy occurred. Sometimes such a patient will, by the completion of term, entirely arrest her tuberculosis, to become more symptomatic after the birth of her child, and again be relatively or entirely free from active tuberculosis during successive pregnancies. It is the writer's opinion that no tuberculous woman, becoming pregnant, should be aborted on principle, if she has a history of being manifestly improved since the onset of pregnancy, or especially if a tuberculous multipara presents an experience of abatement of tuberculosis during a previous pregnancy. It is likewise doubtful practice to abort a patient with very far-advanced tuberculosis; for a large proportion of such patients will undergo spontaneous abortion. Numerous instructive cases, illustrative of the above condition and principles, occur to the writer, but the requirements of space forbid their citation in a paper of the present scope.

In summary, then, what are the known *facts*? They are, first, that pregnancy operates in widely divergent fashion on nontuberculous women, that is, it may uplift and it may depress the individual economy; second, that pregnancy works to similar effect in tuberculous women, that is, it may arouse and it may quiet active tuberculosis. There have been numerous contributions to the general thesis that actively tuberculous women have their tuberculosis improved during pregnancy. In respect, then, to this bilateral effect of pregnancy on tuberculosis there will, no doubt, be general agreement among the informed.

Why, then, this pother and uncertainty? For any difference of opinion could be concerned only with what might be called quantitative effects, that is: Does pregnancy harm the tuberculous woman more frequently than it benefits her; and, if so, how much more?

Before attempting to answer a problem, so insoluble on the basis of the data at hand, the writer begs permission to make one suggestion, as perhaps worthy of consideration in attempting a solution. He would put this in the form of a question, as follows: May it not be that pregnancy exerts a harmful effect on tuberculosis in those women who, without tuberculosis, would naturally tolerate pregnancy poorly, and a harmless or even beneficial effect on those tuberculous women who, without tuberculosis, would stand pregnancy well or even have their bodily

economy improved by pregnancy? An inquiry conducted along such lines might prove fruitful. And relative proportions of activation and arrestment should be compared with obstetricians' reports of the same proportions of women, well or poorly tolerant to pregnancy. Yet, even here, due and, maybe, decisive allowance might have to be made for the broad circumstance that people—women—in health are not accustomed to consult physicians and thus come under their surveillance.

Before concluding, one word more.

We have long been hearing much as to how pregnancy may or may not affect tuberculosis, but the effect of tuberculosis on pregnancy has attracted little attention. What may or may not tuberculosis do to pregnancy; and could or might tuberculosis influence pregnancy in such a way as to have the latter react back upon tuberculosis favorably or unfavorably? Of course, we have long known that far-advanced tuberculosis tends to induce abortion in both women and cows. But can or does it exert any other significant or decisive influence?

Who knows? Yet speculation is rather intriguing.

On the one hand we know that, as pregnancy is set in motion and as it moves along to a climax, parturition, the puerperium and lactation, profound and vast and inextricably interlocking changes throughout the endocrine domain come into play. Even the ancient Romans had discovered an early change, as depicted in their custom of ribboning the bride's neck and detecting pregnancy later as the neck-band began to tighten. It is likely that pregnancy induces in all large mammals the most extensive orderly alterations of general endocrine function that occur episodically during life,—and these, as it were, upon the "pull of the trigger."

With this broad fact, consider whether and how tuberculosis may affect endocrine function,—and thus perhaps pregnancy.

In not a few persons, suitably constituted and predestined by constitution, tuberculo-intoxication surely spurs on the thyroid,—wherefore a not uncommon difficulty in the differential diagnosis between pulmonary tuberculosis and exophthalmic goitre of minor degree.

Tuberculosis stunts growth in many children. Does it do so through the hypophysis? Or again through the hypophysis, when we finally arrive at the *habitus phthisicus*, of gracile, tall and slender frame, and extremities disproportionately long as to torso.

For a century and more it has been suggested that tuberculosis stim-

ulates orchidal activity, but this has been difficult of authentication and has been strenuously denied.

That tuberculosis lowers blood-pressure is beyond doubt. But, does it do this through the adrenal or through its general atonic influence on the capillary bed? Or, through what agent or agency does tuberculosis depress muscular tone?—through the adrenal?

But, among the best-authenticated of the minor effects of tuberculosis is its influence on the menses, making these scant and abnormal in other respects. Is this action circuited by way of the thyroid?—Hardly. For, if so, we should expect rather a tendency to menorrhagia. Through the ovary?—Perhaps.

If tuberculosis can and does influence ovarian activity, it is at once conceivable that it may have a variable effect upon the course of pregnancy. How, and toward what result, we do not know. We do know, however, that it is a potent activator of spontaneous abortion: again how and through what channels we do not know.

At any rate, we might well keep alive to the possibility of interrelationships and reciprocal relationships between tuberculosis and pregnancy. Perhaps, even, we may now and then have the ground prepared for the formation of a "vicious cycle" as concerns the two states.

A. K. K.

THE ARCHITECTURE OF THE TERMINAL SECTIONS OF THE BRONCHI OF THE HUMAN LUNG

The Pulmonary Acinus[1,2]

WOLFGANG GRETHMANN

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1. INTRODUCTION

Notwithstanding all efforts and investigations, we are still lacking a clear and unequivocal description of pulmonary architecture, and especially of the subdivision of the finer bronchial endings. The findings of various authors vary greatly, and are even contradictory, depending upon the material used for this study and its technical approach. A most abundant nomenclature only helps to increase the confusion. It is in fact astonishing to notice how little of the knowledge obtained through the investigations of W. S. Miller, Laguesse, Loeschcke, and Husten has been appropriated by the medical world in general, with the resulting loss of a clear conception of the finer bronchial endings and their structure. This fact obviously finds satisfactory explanation in the difficulty of illustrating three-dimensional formations. Thus, reconstruction models and schemes were utilized to clarify the conditions. Because of their unhandiness and liability to breakage, reconstruction models are

[1] From the Pathological Department and the Tuberculosis (Columbia University) Service of Bellevue Hospital, New York City.

[2] Aided by a grant from the Josiah Macy, Jr., Foundation.

available only to a very restricted number of those interested in this particular study. Nor do they illustrate the details of structure, except in an incomplete fashion if, indeed, at all. Schemes are still less reliable in this respect. And all this presupposes that both these methods of illustration represent an exact picture of the anatomical conditions of the human lung, an assumption which is by no means always true.

Attempts to correlate the greatly variable clinical forms of tuberculosis, with their anatomical aspects, gave rise to various systems or classifications of pulmonary tuberculosis, of which the system of Aschoff-Nicol seems to have gained a most lasting significance. It revolves around the concept of the "pulmonary acinus:" that is, the terminal morphological and functional unit of the pulmonary parenchyma, as introduced into pathology by Rindfleisch in 1871. It is in the "acinus" where, according to the above authors, take place the productive and exudative processes of pulmonary tuberculosis. The work of Graeff and Kuepferle constitutes an attempt to read these forms from the roentgen plate.

Besides the "pulmonary acinus," as studied and described by Aschoff's school, especially by Husten, we have the concept of the French anatomists, E. Laguesse and d'Hardiviller. It is most noticeable, however, that although these French authors, too, adhere to the conception of the "pulmonary acinus" of Rindfleisch, which was introduced into French literature by Charcot, they conceive under "pulmonary acinus" something different and more restricted in size. This difference in the conceptions of the two schools is obviously due to differences in the fundamental anatomical conceptions of the "acinus." Therefore it becomes necessary here to discuss the respective meanings of this term.

2. THE TERMINOLOGY OF THE PULMONARY ACINUS

The concept "acinus" has been taken over from normal histology where it has always played a rôle in the classification of the glands. It has been used however at different times with different meanings by various authors.

A glance into the text-books shows the following: According to Maximow and Bloom there exist three types of terminal sections of glands:

If the glandular cells line the wall of a cylindrical, branched or unbranched, usually blindly ending cavity, it is a *tubule;* if they line a spherical or oval sac

with a conspicuous free lumen, it is an *alveolus*; and if the terminal portion has the form of a round or oval body with a narrow lumen and is attached to the excretory duct in the fashion of a berry hanging on its stalk, it is an *acinus*. . . . The form of the terminal portion, however, if taken as the sole criterion, does not give a satisfactory classification. The general architecture and structure of the organ must always be taken into consideration.

Stoehr-v.Moellendorff's classification is similar to the above. He classifies the glands according to their lumina, either as tubular or as alveolar. He also considers the external shape, however, and distinguishes among the great number of tubular glands the so-called "tubulo-acinous glands." If viewed from the outside, one sees attached to the endings of the tubular system spherical to club-shaped acini (berries). The acinus distinguishes itself from the alveolus only in that it is bulbous, enlarged externally due to a thicker epithelial cell layer. "The lumen of the acinus is just as narrow, however, as that of the immediately preceding tubular system."

J. Schaffer traced back the origin of the concept "acinus" to Malpighi (1688), who used this term for designating the glandular granules or lobules still recognizable on the preparations with the naked eye; the term was thus used for designating a lobule. Subsequently, it was employed also for designating terminal sections of glands recognizable only under the microscope, and attached to the excretory duct of the last order. Johannes Mueller was the first to distinguish, according to the form of terminal sections, between acinous and tubular glands. After Henle, in 1858, used the term "acini or alveoli" synonymously, erroneously replacing the designation "acinus" by the term "alveolus," which means a small depression or sacculation, Boldyrew suggested dropping the term "acinus" altogether, and to speak of alveoli. In order to prevent further confusion, M. Heidenhain suggested that the term *tubular*, *alveolar* and *acinous* be used strictly according to their respective significance. Accordingly, acinus designates a grape- or berry-shaped element, and relates therefore only to the external shape, irrespective of its lumen; only if the lumen also represents a spherical ampulla- to pear-shaped cavity, should one speak of an alveolus.

The aforesaid shows that agreement is lacking among morphologists as to what an acinus is, some considering the shape of the lumen as the important criterion; others, the external shape. Still other workers, particularly Laguesse, make the definition dependent upon functional characteristics, speaking as they do of the secreting cavity of the gland.

Application of the morphologically unclear and equivocal concept "acinus" to the pulmonary architecture must, therefore, be used with a certain constraint. The authors who made use of this designation can be divided into two main groups, distinguished from one another mainly by the size of the unit to which they refer. To the one group which restricts the limit of the "pulmonary acinus" belong Rindfleisch, Orth, and Laguesse. The other group, which accords it an essentially greater size, is represented by Husten, Aschoff, and Loeschcke.

Disregarding for the moment the details of its structure, etc., which will be dealt with in a later section, we find that the concept "acinus," as applied to the terminal sections of the bronchial tree, is defined as follows by the various workers:

According to Rindfleisch, who introduced this concept into pathology, the branching alveolar passages represent, in their totality, the equivalent of the acinus of acinous glands, and must, therefore, be designated "pulmonary acinus." It is, according to Rindfleisch, a far more constant unit of the pulmonary structure than is the lung lobule, as far as size is concerned.

Orth designates "acinus" as the totality of the parenchyma consisting of the alveolar passages, their infundibula and the alveoli, attached to the end-bronchus "like a berry to its stalk." He designates, as lobules, greater sections of the parenchyma, comprising 9 to 12 or 15 acini.

Since Laguesse understands under "acinus" the secreting cavity of a gland, the respiratory cavity is, according to this worker, a genuine final unit. In it terminate the bronchioles. It is the terminal unit of the lung parenchyma, which, in order to prevent confusion of any sort, he would not like to have designated "lobule."

Au bouquet de canaux alvéolaires, ou plutôt au canal alvéolaire ramifié en bouquet qui fait suite à une bronchiole acineuse, on donne généralement le nom d'acinus (Rindfleisch), comparant cette cavité respiratoire à la cavité sécrétante qui fait suite au dernier rameau des canaux excréteurs dans les glandes. . . . L'acinus est uniquement constitué de canaux alvéolaires, à l'exclusion de tout rameau bronchique.

One would also have to consider here that the acinus of a gland may be either very short, and constitute a simple tube, or very complex, long and branching. It is only to such a complex acinus that the pulmonary acinus may be compared.

Husten, on the other hand, gives the following definition:

If, under acinus, one understands the lobule of a gland, comparing the lung with this terminology to a gland, then all respiratory elements in the lung—corresponding to the secreting elements of glands—must be comprised within the acinus. Accordingly, it would be advisable to include within the acinus all that bears alveoli, be it respiratory bronchiole of the first, second or third order, an alveolar duct or an alveolar saccule. I would suggest, therefore, to have the acinus begin with the respiratory bronchiole of the first order, and to designate the latter, with all its subdivisions, as pulmonary acinus.

According to Aschoff, the acini are the terminal morphological units, where the respiratory bronchioles represent the intercalate portions, intermediate portions (*Schaltstuecke*), while the alveolar ducts and saccules may be compared to the secreting sections of secreting glands, for example.

Finally, Loeschcke lets his acinus begin an order higher, that is, the terminal bronchiole and all its branches. Therefore, when he speaks of an "acinus," he means what Husten would call a double acinus.

The above short review shows, that, while one group of authors (Laguesse) understands under "pulmonary acinus" only the terminal sections, *with exclusion of any bronchial elements, respiratory bronchioles or intercalate portions* (*Schaltstuecke*), *the other group* (*Husten, Aschoff*) *includes these latter elements within the acinus;* in fact, one can almost say, they directly make of them the purport of the concept.

3. THE DEVELOPMENT OF OUR KNOWLEDGE OF THE FINER ARCHITECTURE OF THE LUNG

In 1688 Malpighi demonstrated, by quick-silver injections, that there exist no connections between the blood-vessels and the bronchial tree. In 1822, Reisseisen showed, with the same method, that the bronchial branches gradually decrease in length and diameter, and increase in number toward the periphery, and that under the pleura they dilate, assuming the shape of ampullae, each of which bears on its distal end a single air-cell. According to Reisseisen, therefore, the lung vesicles constituted the terminal blind endings of the tubes.

In order to arrive at a sharper separation between the vascular and bronchial systems, Rossignol, in 1847, injected the two systems with differently dyed masses. Through this improved technique he arrived at conceptions as to the architecture of the terminal sections of the bronchi which are still of fundamental significance for our present-day

knowledge. According to him, the lung of mammals is a conglomerate of a great number of like lobules, attached to the terminal branches of a common bronchial tree. Their form varies from cone-shape to polyhedral shape. In each of these lobules there ends a bronchial branch which reaches the middle of a lobule in a straight course, and divides there into two branches which subdivide again and again to complete exhaustion. These branches of the second to eighth order may run in all directions, centripetally as well as centrifugally, and may cross one another in any direction without ever anastomosing. They gradually become shorter and more numerous the higher the order to which they belong, and, eventually, terminate with an abrupt dilatation having the shape of a funnel. These funnels are composed of polygonal cavities to which Rossignol gave the name of *alveoles pulmonaires*. The latter are distinctly recognizable on section, are separated from one another by partitions, and serve the gas exchange. From five to twelve of these cavities go to form greater hollow prisms, *en entonnoir*, with thicker partitions between them and a round base; for which Rossignol suggested the designation *infundibula*. He considered these as "primitive lobules," and said that they constitute the elementary unit. As a rule, two or three infundibula unite after a short course to a tube which shows, at various levels, openings of other infundibula. Already these connecting tubes bear alveoli in their walls, the number of which increases in the direction downward. (Figure 1.) To-day we clearly understand why Rossignol designated the terminal structures by the name *infundibula: he meant to distinguish completely alveolized structures from the air-supplying system*. Since, in view of our present knowledge, there is no longer any need for this designation, it is desirable that the confusing word *infundibulum* disappear completely and finally from our pulmonary nomenclature.

Rindfleisch starts in his description of the terminal bronchial sections from the lung lobule which is about 1.5 cm. long and 1 cm. wide. (Figure 2.) The bronchus enters the lobule at its root and gives off approximately seven smaller bronchioles within the lobule, each of which bifurcates into two very short bronchioles of the smallest calibre. These open directly upon a group of from three to five branching alveolar ducts which, together, form a pulmonary acinus. A lung lobule may be made up of fourteen to thirty acini. If one enters Rindfleisch's acinus through the lumen of its bronchiole, one comes without any transition upon the mouth of three to five alveolar ducts.

The designation *alveolar ducts*, met with in Rindfleisch's description, had shortly before been introduced into the literature by Franz Eilhard Schulze, who pointed out that the terminal blind sections of the bronchioles no longer represent strong tubes of uniform thickness. They are

FIG. 1

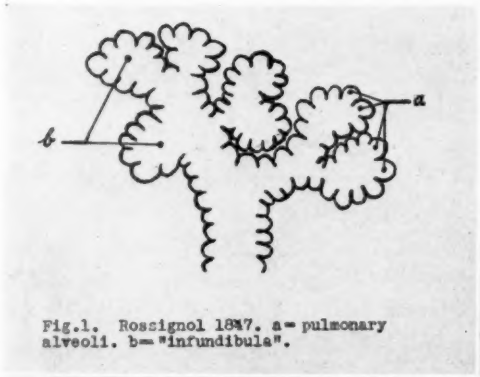


Fig.1. Rossignol 1847. a= pulmonary alveoli. b= "infundibula".

FIG. 2

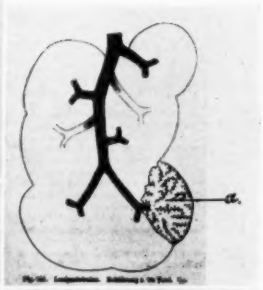


FIG. 3

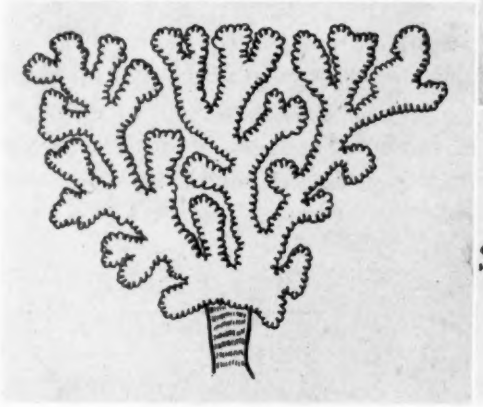


FIG. 4

FIG. 1. Rossignol 1847. a = pulmonary alveoli. b = "infundibula"
FIG. 2. Lung lobule of Rindfleisch. a = Rindfleisch's "pulmonary acinus"
FIG. 3. F. E. Schulze's "alveolar duct system"
FIG. 4. Lung lobule of W. S. Miller 1892. br. = bronchiolus terminalis; d.al. = ductulus alveolaris; a = "atria;" s.a. = sacculi alveolares; a.p. = alveoli pulmonales.

so densely studded with numerous hollow cells, the alveoli, that the walls of the terminal air-passages are formed for the greatest part by the alveoli; that is to say, by the alveolar walls themselves. Figure 3 is an illustration by Schulze of this "system of alveolar ducts." According to this worker, the inner lining of these alveolar passages and alveoli is

formed by a continuous epithelium composed of two types of cells: (1) thin, large and light structureless plates with irregular angulous or slightly wavy outlines, and (2) few polygonal, or irregularly round, epithelial cells, with pale, round nucleus, scattered in between (Elenz). These conceptions of the architecture of the abrupt transition between the smallest bronchioles and the alveolar passages meant a backward step in our knowledge even as compared to the findings of Rossignol. Koelliker, therefore, undertook to study and to clarify the exact histology of these sections of the lung.

His view was that between the terminal bronchiole and the alveolar duct system of Schulze there were interspersed air-passages which contained both bronchial and respiratory elements,—the *respiratory bronchioles*. According to him, the respiratory bronchioles were of two different types: *1: Respiratory bronchioles with uniform epithelium:* These are tubes with uniform, cylindrical, ciliated epithelium, and are continuations of the smallest true bronchi, and differ from these only by the absence of goblet-cells and the presence of alveoli in their walls. They go over into *2: The respiratory bronchioles lined with two different kinds of epithelial cells;* namely, (a) cylindrical or low cuboidal cells and (b) large, polygonal plates. They also bear alveoli lined with the same epithelium as the alveoli of the small lung lobules. This epithelium, which is composed of large, thin, *anuclear plates, and small nucleated squamous cells, Koelliker designates respiratory epithelium.* The bronchial epithelium lining the respiratory bronchioles gradually becomes restricted to an increasingly smaller portion of the wall and eventually ceases altogether. As, with steadily increasing alveolization of the respiratory bronchiole, there arises a respiratory epithelium over the whole wall of a respiratory bronchiolus, we are dealing with "alveolar ducts," of which several issue from each respiratory bronchiole. All alveolar passages still show strands of smooth musculature in their wall, most of which run circularly. Besides, there exists, at the entrance of each alveolus situated in the tubular wall, and at the entrance of each alveolar duct, the appearance of a ring muscle. In the alveolar walls, however, and in the septa separating the blind ends of the alveolar ducts (infundibula), there is no trace of musculature.

4. MODERN DESCRIPTIONS

These are based mainly upon findings obtained with the paraffin technique and the reconstruction methods made possible by this

technique. Here belong the studies of W. S. Miller, Laguesse, Husten, Loeschcke, and Ogawa.

Disregarding the first description of the "lung lobule" by Miller in 1892, in the *Anatomischer Anzeiger*, which he simplified subsequently (*cf.* scheme figure 4), the architecture of the terminal branches would be as follows, according to this worker: Miller subdivides the lung into small segments or lobules. Each lobule represents a terminal section of the bronchial tree, with its air-spaces, blood-vessels, lymph-channels and nerves. In this "unit" the elements are arranged as follows: The terminal branch of the bronchus, which Miller designates *terminal bronchus* = ductulus alveolaris, and which already bears alveoli, dilates somewhat at its distal end before breaking up into the pulmonary parenchyma. From this dilated end-piece of the ductulus alveolaris, three to six fairly round openings lead into approximately spherical cavities, which Miller designates *atria*. Again, sprouting from each "atrium" is a number of greater, and more irregular cavities ("air-sacs") which, on their surface, bear small protrusions ("air-cells"). Miller says literally:

> From this description it follows, that the "air sacs" (infundibula, air saccules) are not, as is usually described, directly connected with the "terminal bronchus" (ductulus alveolaris), but that between each air sac and the ductulus alveolaris there is inserted a cavity, which is regularly found in all parts of the lung, and to which I have given the name "atrium."

In a more recent comprehensive description in his *Harvey Lecture*, in 1924, Miller reaffirmed his earlier description which, as must be strongly emphasized, is *based mainly upon a study of dogs' lungs*. According to Miller, therefore, it would be immaterial whether lungs of cats, dogs or human beings are used for this study. If, on reconstruction, one places the plane of the sections in continuation of the axis of the ductulus alveolaris, one would, according to Miller, invariably obtain the picture illustrated in figure 5, which is taken from his Harvey Lecture.

The outstanding feature in Miller's concept is, therefore, the insertion of the "atrium" between the ductulus alveolaris and the sacculus alveolaris. Ever since its first publication, this conception of Miller failed to meet with general approval. Therefore, a short time later, the same subject was tackled by Laguesse and d'Hardiviller. To these two French authors we owe quite a number of fundamental studies of the architectural conditions of the human lung. Unfortunately, however,

these contributions seem to have completely escaped the attention of W. S. Miller.

Laguesse studied in his reconstructions the macroscopic lung lobule, a far greater unit than did Miller. It corresponds to the "secondary lobule" of Sappey and Miller. Its shape is approximately pyramidal, with four lateral surfaces and the following dimensions: average width of the basis, 13 mm.; height, also 13 mm.; capacity, about 1 ccm. (*cf.* figure 6). At the apex of this pyramid, the bronchus, accompanied by its artery, enters the lobule, the bronchus thus becoming an intralobular bronchus. It descends in a more or less direct course to the basis of the lobule. After having given off several lateral branches (collaterals), it now divides *dichotomously*. The collaterals, arising from the main stem, branch in the upper part of the lobule. Their angles of division are usually acute and directed downward, and but rarely obtuse or directed upward. The number of collaterals is constant, but stands in direct proportion to the length of the stem. From the collateral branches of the intralobular bronchus arise, according to Laguesse, between six to twenty-four terminal or "acinous" bronchi, each of which again give off an "acinus" or bunch of alveolar passages. At a certain level, which Laguesse places in the middle third of the lobule, the intralobular bronchus, which up to now only gave off collaterals, subdivides from here on in a dichotomous manner exclusively into branches of various orders. One invariably finds branches of the first to third order (2–4–8 branches). Only exceptionally does one observe one or several branches breaking up already here into an acinus or terminal bunch of alveolar passages. Normally, the division goes on to the fourth order (16 branches). Even if now some of the branches have already broken up into an acinus, the division continues undisturbed and may proceed to the seventh order (32–64–128 branches). The higher the order, the higher, of course, also the number of acinous bronchi. Each terminal bronchiole divides ultimately into a number of branches (4–6) which are the acinous bronchioles. Hence, according to Laguesse, the number of these acinous bronchioles in a lobule is only rarely less than thirty, and varies in general from between fifty to eighty to one hundred. Of quite special interest are, of course, the structural details of the bronchi and of those sections which form the transition from the former to the real acinus or bunch of alveolar passages. According to Laguesse, the bronchi bear no alveoli, or at least only very exceptionally. Their entire wall is lined with high, crinkled, prismatic epithelium. This epithelium rests upon a delicate

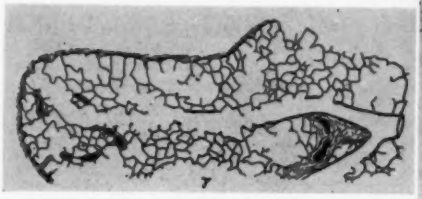
basal membrane, beneath which follows immediately the muscular layer which completely surrounds the canal. The whole is enveloped by a connective-tissue adventitia, and the accompanying artery is likewise fastened to the bronchus through an adventitia. Further down, the longitudinal folds with prismatic epithelium become restricted to that side of the wall along which runs the artery. In the entire remaining part of the wall of the air-passage the prismatic epithelium rapidly becomes flattened out and goes over into "respiratory epithelium;" that is, much of the wall of the tube is lined with alveoli.

It is only to these latter sections that Laguesse would apply the term *respiratory bronchioles*, but he would prefer even to have them named *transitional* or *acinous* bronchioles. They are, according to Laguesse, very short: in one case which he measured, their length was only 130 micra. Succeeding these transitional bronchioles are tubes completely lined with flat respiratory epithelium and alveoli. We are now in the alveolar passages which, after a very short course, in one instance after a stretch of only 100 micra in length, divide in their turn. The passages now become wider and break up dichotomously into a bunch of alveolar passages, *the real acinus*. Laguesse emphasizes the point that the acinus is composed solely of alveolar passages, with the exclusion of any bronchial components. Figure 6a shows the reconstruction model of Laguesse with a bronchiolus terminalis, two orders of "acinous" or "transitional" bronchioli, and the lung acinus proper.

Husten describes the morphological conditions somewhat differently. Figure 7 presents Husten's conception which, as must be said here, is more or less also a scheme, as it is a composite of several different thin sections. He subdivides the respiratory bronchioles, from the terminal bronchus downward, into those of the first, second and third orders. The respiratory bronchioles of the first order present places that are no longer encircled by ring musculature. These places correspond to the insertion of the first alveoli. At the site of origin of the alveoli one still sees distinct ciliated epithelium which, in many instances, even lines the entrance to the alveoli situated in the wall. After further dichotomous subdivisions, in which that part of the wall alongside the accompanying artery still retains a higher epithelium (corresponding to Koelliker's respiratory bronchiole lined with two sorts of epithelium), we have before us the respiratory bronchiole of the second order. The alveoli arising from the wall of the bronchiolus respiratorius increase in number and size, but of course no alveoli arise from that area of the wall along

which the arteriole runs. The columnar and cuboidal epithelium no longer lines the entire circumference, but is restricted to the ridge over the course of the accompanying arteriole. From this ridge strands of

FIG. 5



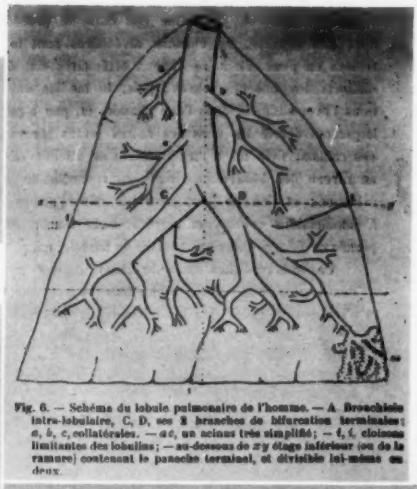


FIG. 6

Fig. 6. — Schéma du lobule pulmonaire de l'homme. — A, Bronchiole intra-lobulaire, C, D, ses 2 branches de bifurcation terminales; a, b, c, collatérales. — a c, un acinus très simplifié; — f, f, cloisons limitantes des lobulins; — au-dessous de x y étage inférieur (ou de la ramure) contenant le panache terminal, et divisible lui-même en deux.

FIG. 6a

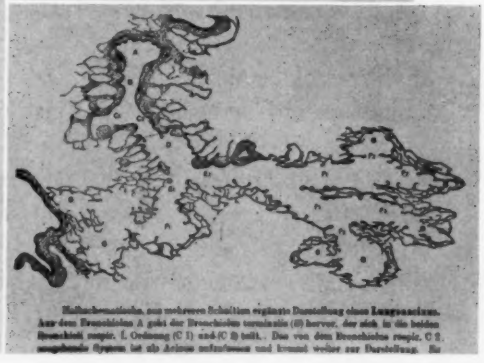


FIG. 7

FIG. 5. W. S. Miller. Harvey Lecture 1924. Longitudinal section through the terminal branches of the bronchial tree, showing, according to Miller, two respiratory bronchioles, a ductulus alveolaris, an "atrium" and an infundibulum.

FIG. 6. A lung lobule of Laguesse with its terminal unit, the "pulmonary acinus" in the lower right-hand corner.

FIG. 6a. Reconstruction model of Laguesse, showing the terminal branches of the bronchial tree: a bronchiolus terminalis (a), two orders of "acinous" or "transitional bronchioles" (b; b), and one pulmonary acinus proper (c).

FIG. 7. Half-schematic picture of Husten's lung acinus: B = bronchiolus terminalis: C1; C2 = respiratory bronchioles of first order; D = respiratory bronchiole of second order of which one is only shown: E1; E2 = respiratory bronchioles of third order: F1; F2 = alveolar ducts; G = alveolar saccules.

muscle fibres and elastic connective-tissue fibres extend through the alveolar bases and encircle the lumen of the respiratory bronchiole. After a further subdivision we have before us the respiratory bronchiole of the third order. The epithelialized ridge becomes narrower and flatter; the alveoli become larger and more numerous. Musculature is still demonstrable alongside the arteriole. It encircles, together with strands of elastic fibres, the alveolar bases, and, coursing between the alveoli, it encircles the respiratory bronchioles. At a certain level of the respiratory bronchiole of the third order the cuboidal epithelium ceases, and the bronchiole loses its character as a respiratory bronchiole and breaks up into a system of alveolar passages. At this site, two or more (up to five) alveolar ducts arise, but, because of the shortness of the alveolar passages as compared to their relatively great width, it would be difficult to discern whether two passages issue simultaneously from the end of the respiratory bronchiole of the third order, or whether they originate from a common alveolar passage which is very short and divides dichotomously immediately after its origin. Husten emphatically distinguishes between alveolar passages and "alveolar saccules." The former are tubes lined all round with alveoli and dividing still further, while the latter are terminal saccules, also lined with alveoli. The "alveolar saccules" may also arise directly from the dilated end of the respiratory bronchiole of the third order, in the same way as the alveolar passages. The alveolar passage is still encircled by bundles of muscular fibres running in circular arrangement, and by a system of strong elastic fibres, without there being always formed a complete ring. In the "alveolar saccules," the ring of elastic fibres around the alveolar basis is still demonstrable, whereas muscle fibres are usually no longer observed here. This mode of the division of the respiratory bronchiole is, according to Husten, an absolute rule, yet one might observe isolated places where alveolar passages and saccules arise immediately from the course of a respiratory bronchiole of the second or third order. Depending upon the size of the lobule and, consequently the space available for division, the individual sections would show great variations in length and distinctness of development.

Loeschcke has his *bronchiolus terminalis verus* divide dichotomously into two respiratory bronchioles, from which arise the alveolar passages of the first and second, sometimes also of the third order. The alveolar passages end blindly on the surface of the acinus in the "sacculus alveolaris." The respiratory bronchioles and the alveolar passages bear alveoli, the number of which varies in different acini. The alveolar

passages dichotomize on a plane perpendicular to the respiratory bronchiole, whence the cuboidal shape of the acinus. All acini have rectilinear, flat outlines which sharply delimit the individual acinus from neighbor acini. Adjacent acini, belonging to the same bronchial branch, form groups distinguishable from similar groups belonging to other bronchial branches by sharply rectilinear, flat outlines. In final analysis, therefore, the lung is found to be composed of a multitude of smaller and greater units, well delimited from one another by rectilinear, flat outlines, yet interlapping in mosaic fashion. It is this arrangement which gives the cut-surface its conspicuously patched aspect. Loeschcke considers only the terminal bronchiole from which two respiratory bronchioles, etc., branch off, to be a true excretory duct. Correspondingly, he comprises in his functional unit (the lung acinus) the terminal bronchiole with all its ramifications. Hence, his lung acinus is equal to two of Husten's. This acinus in Loeschcke's meaning is usually, though not always, delimited from neighboring acini by septa. The fine-patched aspect of the lung surface is produced not only by the outlines of the lobules, but rather by those of the double acini. Only the coarser septa enveloping several fields are interlobular septa. The smaller fields are delimited by the interacinary septa. Between the terminal sections of the respiratory bronchioles belonging to an acinus there never exists, according to Loeschcke, a septum formation.

5. ORIGINAL STUDIES: MATERIAL AND METHODS

The immense practical significance of the terminal sections of the bronchial tree made it seem desirable to the author to attain by personal studies a better understanding of the pulmonary architecture and to explain if possible the obvious contradictions of various authors.

As to the choice of the technique, it may seem to some readers that only reconstruction methods are suited for such studies, that reconstruction is the ideal method for reproduction of the anatomical conditions. This is by no means always true. Entirely disregarding the laboriousness of the method, the objections against the reconstruction procedure lie essentially on purely technical grounds. Since there are many objections against the use of the reconstruction method even for more solid organs (*cf.* Schaffer in the chapter on glands in v. Moellendorff's *Handbuch*), it is obvious that with respect to the lung the difficulties of exact reproduction of anatomical conditions must increase almost infinitely. Not only is it hardly possible to reproduce details, let alone

delicate histological features: but, if no special precautions are taken, reconstruction models will only lead to wrong conceptions as to the real conditions. Reconstruction can be based only on first-class, and in every respect perfect, serial sections. If, now, these serial sections illustrate the anatomical conditions with sufficient clarity, I see no reason whatsoever to have recourse to reconstruction models. To what extent I have succeeded in proving the correctness of my statements, the reader may judge for himself by the attached microphotographs. Finally, it may be pointed out that to-day reconstruction by drawings, as recommended by Justesen, is generally considered to be the best procedure. The writer has employed this method, illustrating, however, no drawings which he cannot support by microphotographs. Further technical details will not be discussed here.

Another point to which, in the writer's opinion, only a very few authors have paid sufficient attention is the location, in the pulmonary lobe, of the material to be studied. The architectural conditions of the bronchial tree and, consequently, also those of the lung lobules, are essentially influenced by the amount of space available for their growth during the period of their development.

According to our own experience, sections from the middle third of the posterior aspect of the lung, is the portion where the likelihood of finding a mainly straight course of the terminal bronchial branches is greatest.

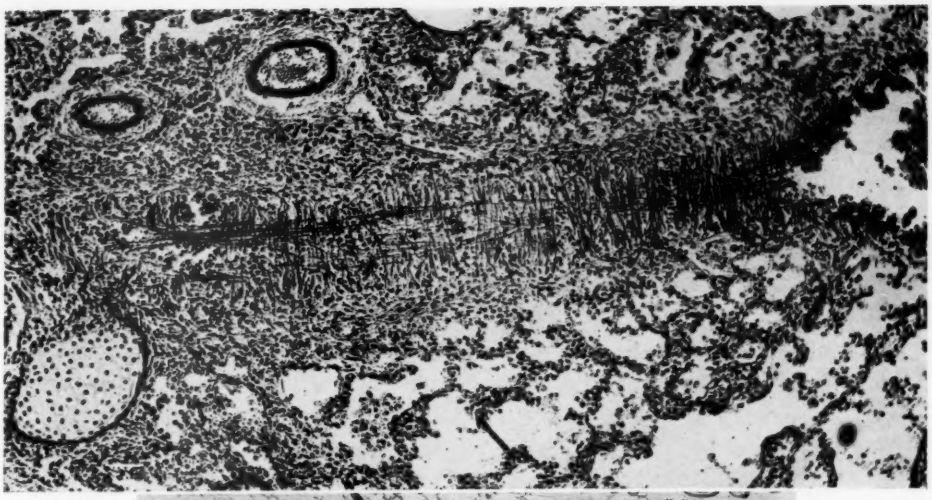
Third, and finally, the choice of the plane of the section as related to the course of the terminal bronchial sections, is important. It would seem most appropriate to choose the plane parallel to the pleural surface. However, it is not easy to follow, with this method, a bronchial branch up to its terminal sections. The method of serial sections parallel to the pleural surface is to a certain degree easily practicable and reliable only up to the transition of the acinous bronchioles into the alveolar passages, whereas afterward it becomes all the more difficult. Or, expressed in other words: so long as one has as a guide the cuboidal epithelium lying over the course of the accompanying artery, it is a relatively simple affair to follow the stem and its lateral branches. After cessation of the cuboidal epithelium, however, one stands rather discouraged before the chaos of alveoli, for as such appear also the alveolar passages to a greater or less extent. An example of this is the work of Husten which remains clear and definite only so long as Husten could follow the cuboidal epithelium, while after its cessation he could establish but few more facts. We shall come back to this point, and to other points of

objection against Husten's method, in a later chapter. One must, therefore, attempt to have the serial sections follow the terminal sections of the bronchioles and alveolar passages, *in their longitudinal course.* Because we know from the investigations of Aeby and His that the terminal branches divide at an angle of about 90 degrees, I placed the plane of my blocks not perpendicular to the pleura, but at an angle of about 45 degrees; the blocks were taken, as mentioned above, from the middle third of the posterior aspect of the lung. Some blocks were also taken parallel to the pleura for comparison. Only human lungs were used as material for study. To obtain absolutely normal lungs for study is not easy. I therefore used routine autopsy material. If, however, a lung showed gross or microscopical pathological changes which would interfere with the finer architecture, it was discarded. The thickness of the serial sections was 6 micra; every second section was studied.

6. ORIGINAL STUDIES: RESULTS

Hardly anything essential can be added to our knowledge of the smaller bronchioles of one-millimetre diameter and less, as established by the corresponding earlier studies of Koelliker and others. The cartilage, the glands and the goblet-cells cease, and all membranes gradually become thinner. In our serial sections, through which, with the aid of microphotograms, we shall study the terminal branches of the bronchial tree, we represent the terminal sections of such a small bronchiole of about 0.6-mm. width. Figure 8 illustrates a tangential section through the wall of another such bronchiole. The submucosa reveals a most intimate network of elastic fibres with a distinct longitudinal and circular layer. From this layer of elastic fibres there extend fine fibres and fibrils to the neighboring vessels, joining and interlaced with the system of elastic fibres of the vascular connective tissue. The cartilage no longer forms a complete ring, but only a cartilage platelet. In its substance one can already recognize very delicate fibrils indicating the transition into fibrous cartilage. The external, very dense, fibrous membrane of the cartilage is, through abundant fibres, particularly closely connected with the fibre-systems of the bronchiole. Further down, the multilayered cylindrical epithelium ceases, its place being taken by a single layer of ciliated epithelium: *we have before us a terminal bronchiole with its subdivisions, as represented by figures 9–14.* The microphotographs show 6 serial paraffin sections of a larger series. The

FIG. 8



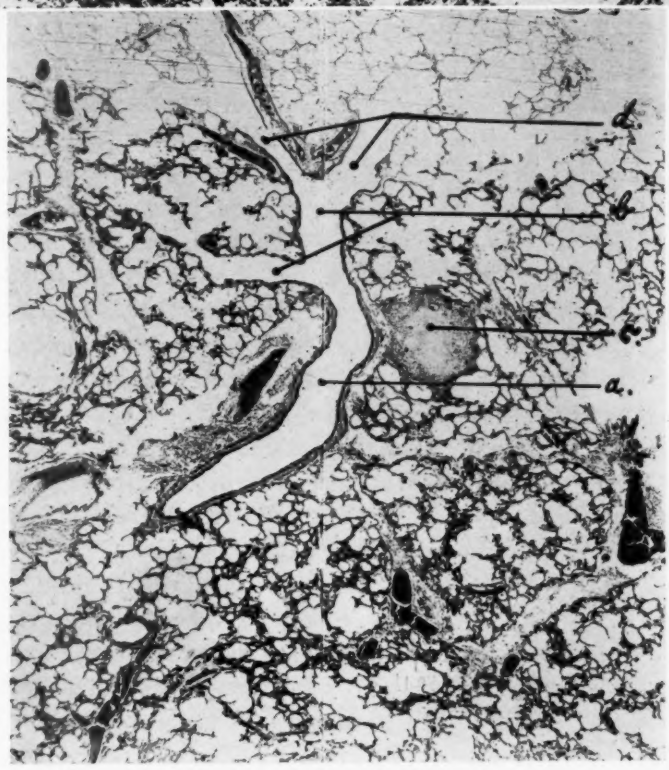


FIG. 9

FIG. 8. Tangential section through the wall of a smaller bronchiole

FIG. 9. Serial longitudinal section 1 of the terminal branches of the bronchial tree. (Microphotograph.) a = bronchiolus terminalis; b = "respiratory" or transitional bronchioles of the first order; d = "respiratory" or transitional bronchioles of the second order; c = miliary tubercle.

thickness of the single section measures 6 micra. Every alternate section was chosen, so that the planes of the sections follow each other at a difference of level of 12 micra. Figures 15, 16 and 17 represent photostatic copies of colored drawings from the slides, made from slides figures 11, 12 and 13.[3]

The structure of a terminal bronchiole is as follows: a single layer of ciliated epithelium resting upon an indistinct basal membrane; the submucosa with relatively well-developed longitudinal, and less well-developed circular, layers of elastic fibres, which intertwine intimately. Beneath the submucosa is a well-developed muscularis. The elastic fibres of these bronchioles are also closely connected with the vascular connective tissue of the interstitium. The bronchiole is accompanied by an artery which, at a deeper plane of our sections, is likewise cut in a longitudinal plane.

The terminal bronchiole then divides dichotomously into two "respiratory" or transitional bronchioles of the first order (*cf.* figure 9), of which the left leads into a different plane. The prismatic, and subsequently cuboidal, epithelium can still be followed for a short stretch in this left lateral branch. Then we see, on one side of the wall, flat "respiratory" epithelium appear in the form of alveoli. In the further course of this left lateral branch one sees, at the site where the artery is attached to the wall, high prismatic epithelium. Sections from planes above and below the illustrated sections confirm our view that we are dealing with a somewhat oblique section of a "respiratory bronchiole."

At the site, now, where the slightly obliquely cut artery is seen in the wall of the left "respiratory" or transitional bronchiole of the first order (figure 9), the latter divides, though at a different plane, into *two respiratory bronchioles of the second order*. One branch runs in the direction toward the reader, the other away from him (oblique section of the artery), and, after a short course of only 85 micra in length they break up into alveolar ducts and the real acini of Laguesse. At a lower plane, about 36 micra below the plane of the section illustrated in figure 9, the division of the "respiratory" or transitional bronchiole of the second order into two alveolar passages is contained in the section. One of these alveolar passages was seen to break up into six terminal ducts, whereas the other represents a straight tube. At a higher plane, about 30 micra above the plane of the section shown in figure 9, the "respiratory" bronchiole of the

[3] For these most beautiful drawings I am very much indebted to Doctor E. Maier.

second order was likewise found already to break up into two alveolar passages and to dichotomize still further, ending up in eight terminal ducts. The branches of this "respiratory bronchiole" of the second order, if we choose this designation, arise, therefore, at about a right angle to the "respiratory bronchiole" of the first order, whereas the course of the alveolar passages with their terminal ducts is again almost perpendicular to the course of the respiratory bronchiole of the second order.

But let us return once more to the main branch of the left respiratory bronchiole of the first order in figure 9. At the site of the slightly obliquely cut artery, we see two alveolar passages arise which both belong to the respiratory bronchiole of the second order. While one of these alveolar passages runs in a general direction upward and to the left, breaking up into terminal ducts delimited by a septum, the other turns, as it were, around the artery, and runs in the direction toward the point of origin of the left respiratory bronchiole of the first order. It here breaks up, in like manner, into terminal ducts which are not, however, all visible on the illustration.

Let us now survey as a whole the just analyzed respiratory bronchiole with its further offshoots. We have before us a three-dimensional formation, similar to that described by Loeschcke as "cube," by Laguesse as "bouquet respiratoire" and by W. S. Miller as "lobule." It is delimited by septa. The picture presented here, whereby we can follow the "canal system," permits clear distinction of a bronchiole of the first and second orders breaking up subsequently into the alveolar passages and the terminal ducts, the latter both composing the real acini of Laguesse. The relative shortness of the respiratory bronchioles, as compared to the alveolar passages and the real acini, is quite evident. This will become still more distinct later. That the alveoli increase in size in the direction toward the terminal sections, as was pointed out by several authors, has not been observed with unequivocal distinctness in our own preparations. A conspicuous feature is the variable length and size of the alveolar passages, and the variable size of the alveoli at different levels of the same canal system. This might be, to a great extent, the expression of growth restriction imposed by the space available for the development. A particularly marked narrowness of the canal system of the terminal bronchiole, or of the respiratory bronchiole of the first order was not observed by the writer. An "atrium," such as W. S. Miller claims also for the human lung, was not observed by the

writer in the here closely followed and clearly discernible canal system of the respiratory bronchioles.

Let us now follow the right branch of the "respiratory bronchiole" of the first order, as presented by figures 10 or 11 and 12. As compared to the left, it seems to continue the course of its stem. Its wall is lined by cylindrical or high cuboidal epithelium, yet one already notices a flattening of the latter and we meet places lined with flat epithelium. In its left wall we now see clearly and distinctly the first alveoli appear. Figure 18 shows how the high cylindrical epithelium bends over into the entrance of the alveolus, while the alveolar base is lined with "flat respiratory epithelium." The alveolar lumen contains a few desquamated alveolar epithelial cells. In the right wall, the alveolization of the wall, while not very conspicuous in our illustration, is yet well recognizable. A conspicuous feature is, however, that *after a very short course, which in length does not exceed the width of its lumen, the "respiratory bronchiole" of the first order divides again dichotomously. We have thus arrived in the area of the respiratory bronchioles of the second order* (*cf. figures 11 and 12*). Here again, one of the branches, in this instance the left, seems to continue the general direction of its stem, whereas the right branch appears as a lateral branch. The wall of this right branch of the second order no longer shows as high an epithelial lining as we still saw a short stretch before. The number of alveoli here is somewhat larger than before. On the right side of the wall a small vessel is visible. Further down, two small lymph-vessels and a small amount of lymphoid tissue can be distinguished. The left wall of the air-passage is accompanied for a short stretch by an arteriole which shortly before had divided into two branches to supply the two respiratory bronchioles of the second order. In that portion of the "respiratory bronchiole" which is accompanied by the artery, the bronchial epithelium is again higher, while beyond the artery it soon flattens out and is also interrupted by alveoli: *we are in an alveolar duct.* The length of this alveolar duct amounts to about three times the width of the "respiratory bronchiole" of the second order. It dilates cone-like, with the point of the cone directed toward its site of origin. *After further dichotomous division it breaks up into the terminal ducts or real acini of Laguesse.* Comparison of the various illustrations shows distinctly that, here also, we are dealing with a somewhat oblique section.

Up to now I have avoided, for good reasons, speaking of "alveolar saccules," although this designation seems to be very well rooted in the

FIG. 10

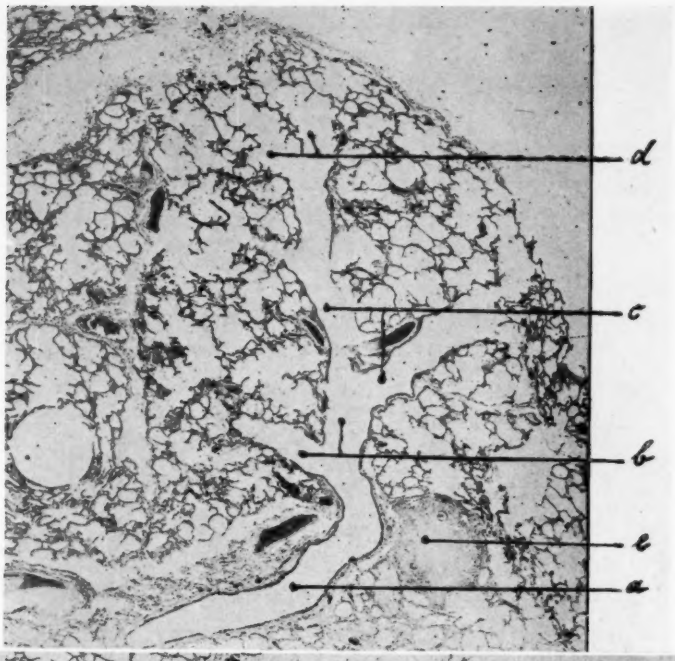


FIG. 11

FIG. 10. Serial longitudinal section 2 of the terminal branches of the bronchial tree. (Microphotograph.) a = bronchiolus terminalis; b = "respiratory" or transitional bronchioles of the first order; c = "respiratory" or transitional bronchioles of the second order; d = alveolar-duct system of pulmonary acinus proper; e = miliary tubercle.

FIG. 11. Serial longitudinal section 3 of the terminal branches of the bronchial tree. (Microphotograph.) A bronchiolus terminalis, two "respiratory" or transitional bronchioles of the first and second order and the alveolar-duct system of the lung acinus proper. For detailed legend see figs. 9 & 10.

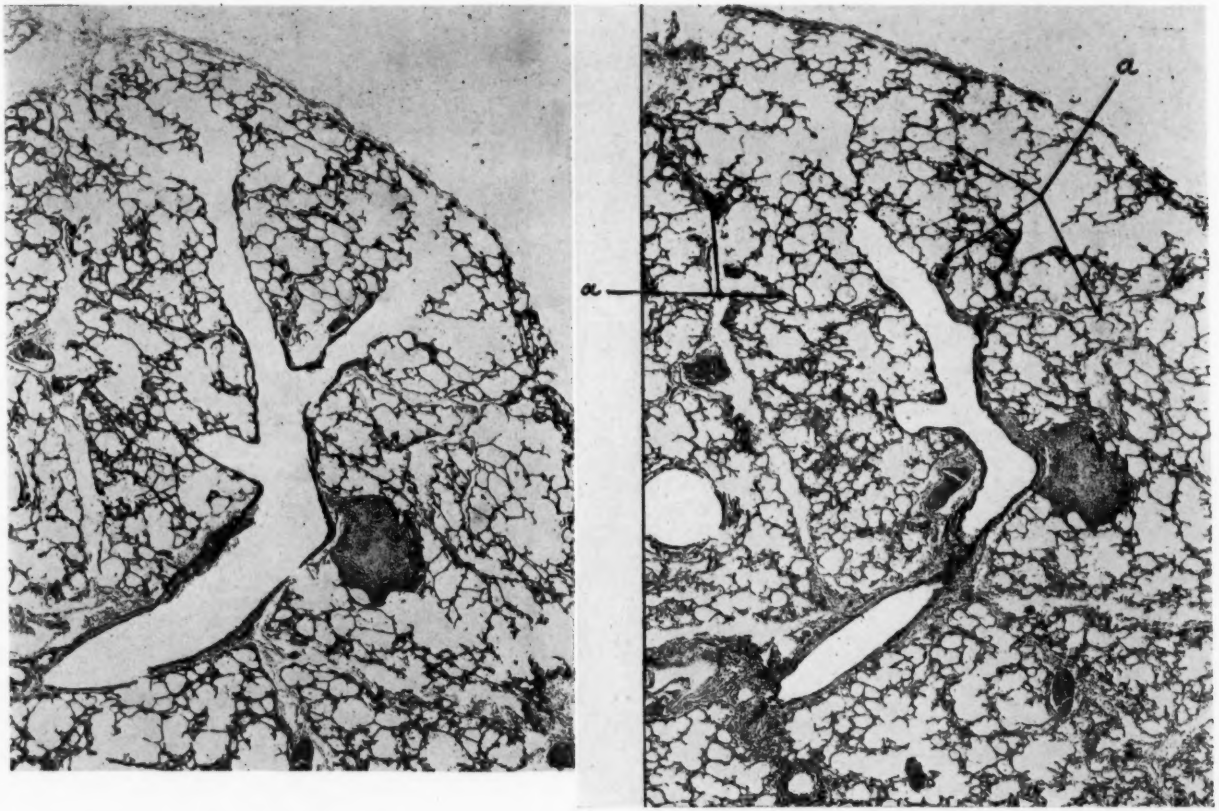


FIG. 12 FIG. 13

FIG. 12. Serial longitudinal section 4 of the terminal branches of the bronchial tree. (Microphotograph.) For detailed legend see figs. 9 and 10.

FIG. 13. Serial longitudinal section 5 of the terminal branches of the bronchial tree, showing especially well the septa interacinaria (a) besides other details. (Microphotograph.)

literature. When looking at the terminal ducts issuing from the right respiratory bronchiole of the second order (figures 11 and 12), one might indeed feel inclined to speak of "alveolar saccules." *In reality, however, we are not dealing with "alveolar saccules," but have before us a small "omission error" which is difficult to avoid with the paraffin technique.* In other words, as we shall see also with respect to the left branch of the respiratory bronchiole of the second order, everything points to the fact that the septum or a part of it between the alveolar ducts, has dropped out, whereby "alveolar saccules" are simulated. Whether, and to what extent, other workers were led by technical conditions to assume the presence of "alveolar saccules," is impossible for me to state.

The left branch of the respiratory bronchiole of the second order remains now to be discussed. Issuing from figure 11, we see at first glance that it is longer than the right branch of the second order. It must stretch itself through the space occupied by the left respiratory bronchiole of the first order and its branches, in order to reach the more distal space, under the pleura, assigned to it for its terminal sections. Figure 9 shows furthermore an arteriole running along the wall on either side, such as was described also by other workers (Laguesse). So long as the arteriole courses along the wall, the epithelium remains cuboidal. Afterward (on the right side at the level of the alveolar duct) it flattens out, without, however, immediately going over into genuine respiratory epithelium. This appears only more distally. The vessel is rather large and its wall comparatively thick as it courses along the alveolar passage. It might seem doubtful whether the vessel on the left side of the tube (figure 9) is really an "accompanying artery." It courses along the respiratory bronchiole of the second order only for a very short stretch, and, after this, to reach in a straight course the area supplied by this respiratory bronchiole and to break up into its terminal branches. Even after the vessel has left the wall of the respiratory bronchiole of the second order, the epithelium still remains cuboidal for a stretch, and then gives way to alveoli. *From the left "respiratory bronchiole" of the second order there arise now (figure 9), by dichotomous subdivision, two alveolar passages.* The left one (figure 9) courses in a general direction toward a rather thick septum. In this septum several veins are seen to unite to a thick trunk (figure 9). It then branches in the direction toward the pleura, as well as in the opposite direction. The right alveolar passage of this "respiratory bronchiole" of the second order appears as a straight continuation of its stem. It then (figures 11 and 12) breaks up dichotomously into

its terminal ducts. "Alveolar saccules" are visible at no place; we rather see distinctly and unequivocally that we are dealing with a canal system of narrower alveolar passages. The indentation in the left wall of the alveolar duct in figure 11 is not an "atrium," but is a tangential section of an alveolar duct as pictured in and described for figure 9 above. Surveying as a whole the above-analyzed right branch of the "respiratory bronchiole" of the first order with its branches, we see that it also represents a three-dimensional formation. It subdivides dichotomously into two "respiratory bronchioles" of the second order, and these, in their turn, break up into alveolar passages. The latter dichotomize further into various directions of the space available, and comprise the real acini of Laguesse. These acini represent a canal system of narrower alveolar ducts; the aim of the complete alveolization of the bronchial tree is attained. The length of the alveolar passages varies, but is in all instances greater than that of the "respiratory bronchioles." The width of the canal system increases somewhat up to the real acini. A cavity similar or corresponding to the "atrium" of W. S. Miller, which would be situated between the alveolar passage and the "alveolar saccules," could not be visualized by the writer although the canal system can be easily followed in its ramifications as described above.

Besides the epithelial lining of the canals, the tunica muscularis attracts our special interest. Its thickness is seen to decrease everywhere in the direction toward the periphery. The well-developed musculature, consisting of muscle bundles running in more transverse or oblique direction, or crossing one another, spans over the entire wall of the respiratory bronchiole. In the respiratory bronchioles, then, the alveoli emerge through this network, and, depending upon their number and size, the meshes of the net become loosened. The net-like arrangement of the musculature becomes thereby all the more conspicuous. On transverse sections of respiratory bronchioles one sees, then, on the side of the wall along which the accompanying artery courses, an almost continuous muscle layer, while, on the opposite side, the bases of the alveoli opening into the lumen show button- or bud-like thickenings due to the bundles of muscle and elastic fibres coursing within them. In the alveolar passages, these septa, protruding into the lumen like buttons affixed to their walls, are even more numerous and more conspicuous. It is through these bundles of muscles and elastic fibres, which surround the alveolar bases and are connected with other bundles encircling the alveolar passages in annular form, that the wall of the alveolar passage receives

FIG. 14

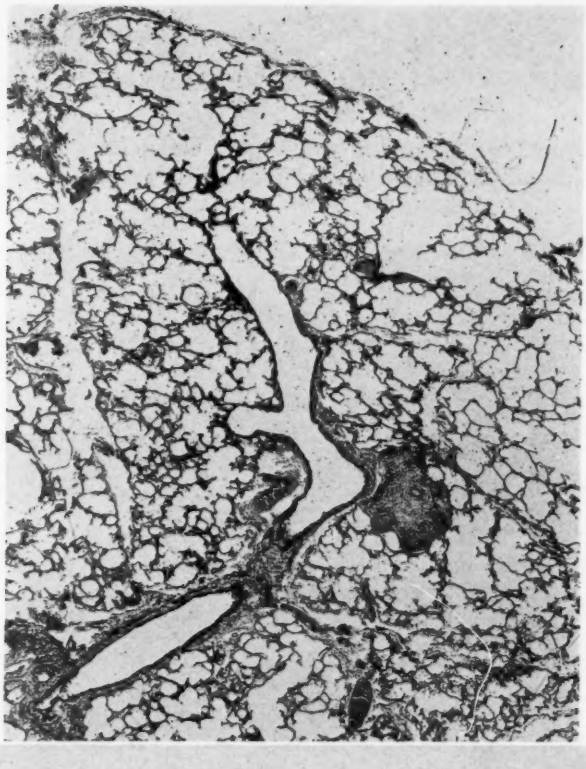


FIG. 18

FIG. 14. Serial longitudinal section 6 of the terminal branches of the bronchial tree. (Microphotograph.) For detailed legend see previous figures.

FIG. 18. Enlarged microphotograph of the wall of the right branch of the "respiratory" bronchiole of the first order. The bronchial epithelium enters the alveolus in the wall of the "respiratory bronchiole." At the bottom of the alveolus desquamated alveolar epithelium cells are to be seen.

its main support. In the distal portions of the acinus, however, I have not encountered muscle fibres clearly distinguishable as such.

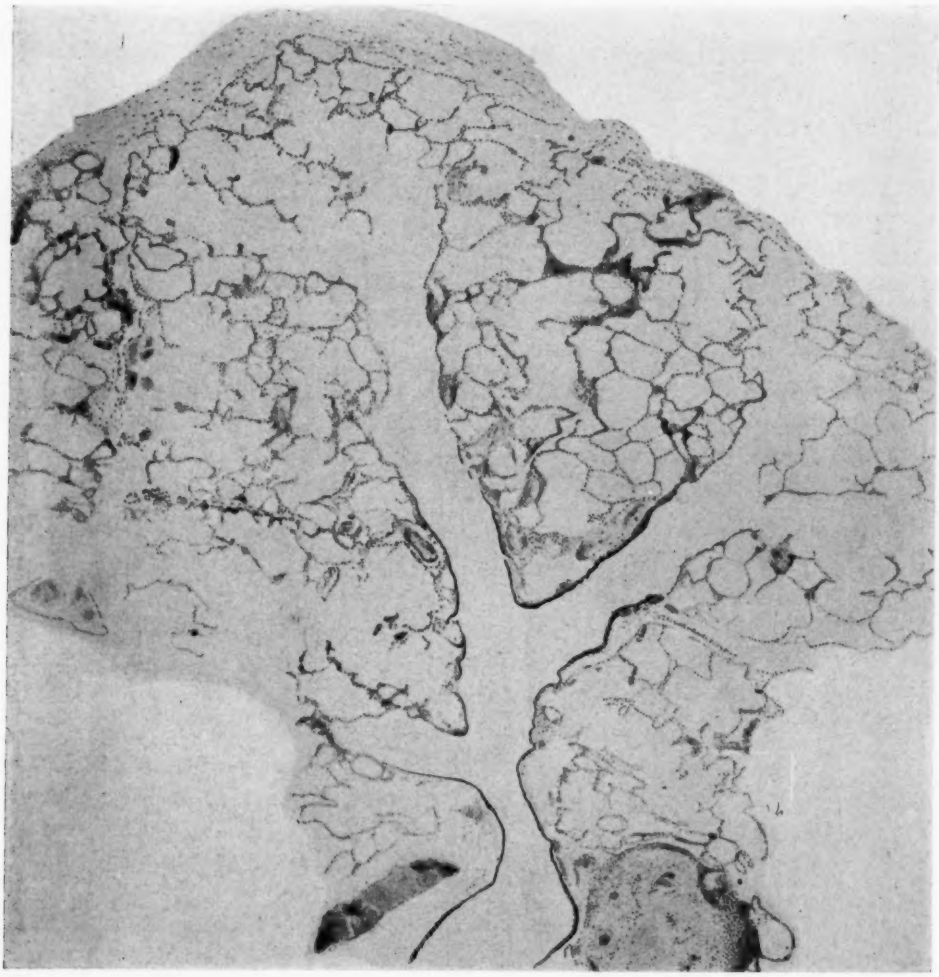


FIG. 15. Photostatic copy of a drawing of serial longitudinal thin section 3. Fig. 11 represents the microphotograph. For legend see figs. 9 & 10.

Like the other two elements—the epithelium and the musculature—the mass of connective tissue, consisting of collagenous and elastic fibres, also decreases in the direction toward the periphery. Yet, it persists to a greater extent than the musculature. The alveolar bases are still

distinctly encircled by rings of elastic fibres. These basal elastic rings are in distinct connection with other fibroelastic systems surrounding the sections and with the fibroelastic systems of the interstitium.

In this connection, a word about the division or subdivision of the terminal bronchial sections by connective-tissue septa is well in place.

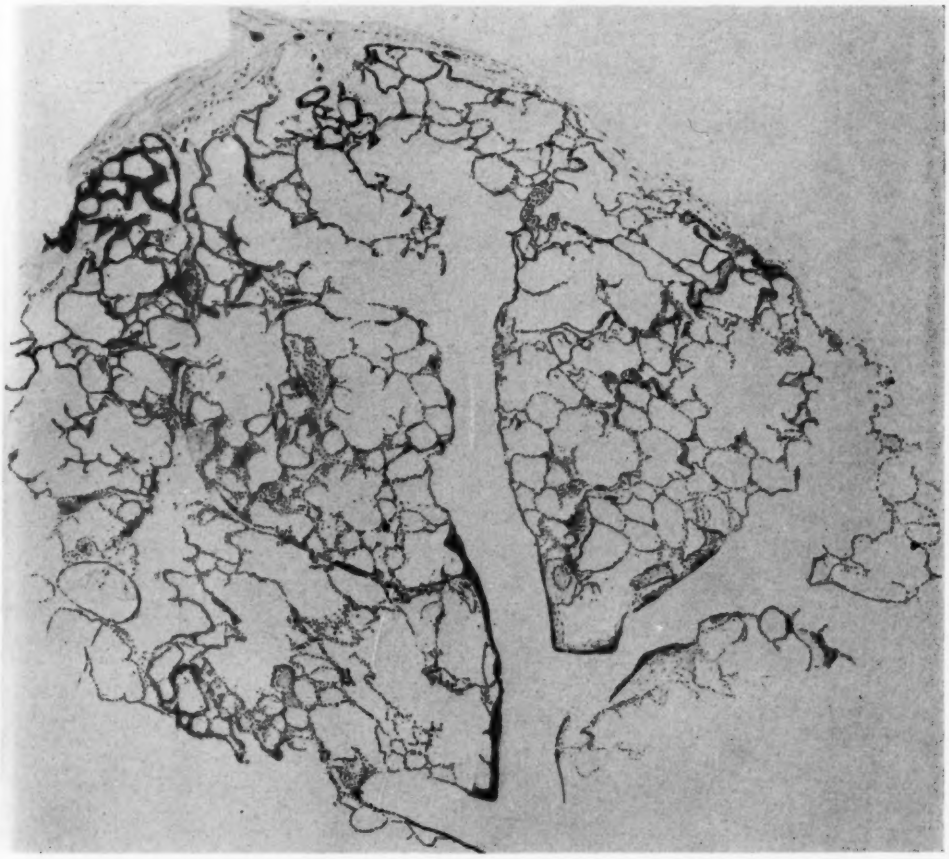


FIG. 16. Drawing of serial longitudinal thin section 4. Fig. 12 represents the microphotograph. For legend see figs. 9 & 10.

The photograms of the sections show with all desirable distinctness that each system of terminal ducts or real acini of Laguesse is enveloped by a very thin and delicate, and occasionally fenestrated septum interacinare. This is quite particularly conspicuous in figures 12 and 13. Again, several acini with their respective air-passages, are held together by thicker

septa. Of quite special significance is, however, the fact, that the more delicate septa interacinaria all *originate at the site of the respiratory bronchiole where the cuboidal epithelium flattens out and goes over into the respira-*

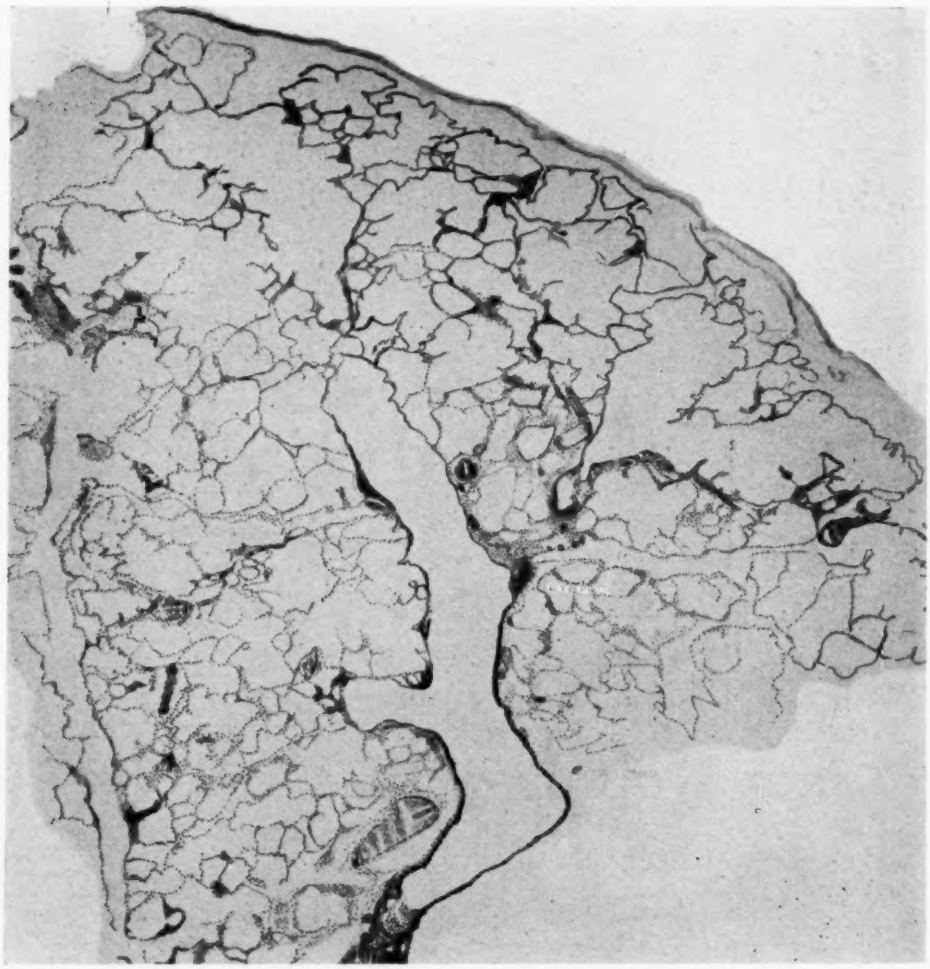


FIG. 17. Drawing of serial longitudinal thin section 5, showing especially well the septa interacinaria. Fig. 13 represents the microphotograph.

tory epithelium of the alveolar duct. The photograms show furthermore that this is also the place where the accompanying arteries subdivide into smaller branches, an anatomical fact which seems to have an important

significance to the writer. It will be discussed at greater detail in a later section.

The pictures show that the area occupied by an acinus may vary in size as well as in shape. This, as I have already pointed out repeatedly in earlier passages of this paper, is conditioned mainly by the space available for their development. That this is valid, however, not only with respect to the real acinus, but also with regard to greater areas occupied by the terminal bronchiole, is obvious from figures 19 and 20. They also show the terminal sections of the bronchial tree, from the terminal bronchiole downward. These terminal sections were taken from an area situated about 1.5 cm. beneath the pleura. It is not difficult to recognize in these illustrations also the subdivisions into the terminal bronchiole, the transitional bronchioles of the first and second order, the alveolar ducts and the real acini, as they are quite distinct. Again, the shortness of the transitional bronchiole of the first and second order is conspicuous. That, in spite of similar architecture, the impression produced is different from that of the terminal sections analyzed further above, can probably likewise be explained by differences in the space available for development.

The description and illustration of transverse sections can probably be dispensed with here, as such pictures have been described by other workers, without there being anything essential to add.

7. DISCUSSION

After having given, in the foregoing paragraphs, an insight into the architectural conditions of the terminal sections of the bronchi and their finer structure, we are again faced by the questions: (1) What is a pulmonary acinus? (2) What is the relation of the acinus to the pulmonary lobule? and (3) Which is the terminal morphological and functional lung unit?

If we briefly return to the discussion in section 2, on the terminology of the acinus, we see, that the concept *acinus* has been defined differently at different times. While some made the concept dependent more upon the external shape, others considered functional criteria as important. However, probably most of the authors who have dealt with the morphology of the glandular acinus, understood under this term only the *terminal sections* of the glands, into which the excretory ducts of the last order lead. Of late, the most consistent representative in this respect seems to be Laguesse. To him, the acinus is the secreting cavity; the

pulmonary acinus, therefore, the respiratory cavity, whether it consists of a simple tube, or of a very complex canal system. Accordingly, the pulmonary acinus is represented by the system of alveolar passages, *with the exclusion, however, of any bronchial components.*

Husten, Aschoff, and Loeschcke allot to the concept an essentially greater scope. They let the terminal bronchiole subdivide into respiratory bronchioles of the first, second and third orders, alveolar passages and "alveolar saccules." Husten's acinus comprises everything beyond and including the bronchiolus respiratorius of the first order. Loeschcke's acinus comprises everything beyond and including the terminal bronchiole. It is thus evident that Loeschcke's acinus is twice as large as Husten's. Aschoff considers the acinus as the terminal morphological and functional unit. According to his definition, the respiratory bronchioles are the "intercalated portions" (*Schaltstuecke*), while he compares the alveolar passages and the "alveolar saccules" to the secreting portions of the secreting glands. As to the description of Husten, it would be difficult to suppress certain objections. Those of technical nature have already been discussed in section 5, to which I refer. It has been pointed out there briefly, that sections cut parallel to the pleural surface, are not, in our opinion, particularly suited for distinct illustration of the anatomical conditions in question. From Husten's presentation one gains the impression that the various respiratory bronchioles constitute canal systems of considerable length. According to my own findings, however, this is not at all the case. I completely coincide in this regard with Laguesse who repeatedly pointed out the shortness of the respiratory bronchioles and prefers to use the term "transitional bronchioles." Subdivision into respiratory bronchioles of the first, second and third order, *which Husten says to be the rule, is not confirmed by my own findings.*

I do not want to go so far as to establish as an absolute rule the subdivision into only two "respiratory bronchioles," although I saw it almost invariably and never encountered respiratory bronchioles of the third order. I have seen longer canal systems than those pictured in the attached illustrations, but I also saw shorter ones; hence, I must maintain that the distances at which the branches of the respiratory bronchioles follow one another *are very short, measuring only micra.* This is altogether in agreement with the findings of Laguesse.

Many authors, particularly again Husten, attribute to the alveoli in the walls of the respiratory bronchioles a special significance in the definition of the pulmonary acinus. As stated before, Husten includes all

"respiratory" elements in his lung acinus, and hence includes the "respiratory bronchioles," since they have alveoli in their walls. But one will be rather disappointed if one expects to find a close relationship between the number of alveoli in the wall of a "respiratory bronchiole" and its order of division, that is, first, second or third order. The ultimate object of the bronchial tree of the lung is the complete and ideal alveolization of its wall. This is merely started in the transitional bronchioles, the length of which may vary, but is, in general, very short. *Accordingly, we find variable conditions in the transitional sections of the same order but belonging to different systems.* It is from this viewpoint that I should like to evaluate the *character* of the alveoli in these transitional sections. Husten and Aschoff are inclined to consider them as genuine "respiratory" bronchioles. Laguesse opposes this view of the respiratory function of these first alveoli arising in the bronchial wall, particularly, among other reasons, because they are supplied by the bronchial artery. We observed and described alveoli in the transitional sections, which we are inclined to consider as respiratory alveoli. On the other hand, however, we have encountered a great many alveoli which, we feel certain, have no functional significance whatsoever. *The opinion as to the significance of these alveoli may, therefore, in good faith remain divided.* When, however, Husten attributes to these transitional alveoli a determining significance in the definition of the concept *pulmonary acinus*, we cannot quite agree with him.

If we analyze the character and the properties of these transitional sections with regard to including them or not in the pulmonary acinus we find quite generally: (1) that they are of variable length but generally very short; (2) that the number of alveoli occurring in their wall also varies; and (3) that their character as "respiratory bronchioles" is disputed by a good many competent workers. *Consequently, all definitions of the pulmonary acinus based upon these criteria, as, for example, those of Husten, Aschoff and also Loeschcke, shall, in our opinion, likewise be unsatisfactory and much disputed.* On the other hand, it must be admitted that the definition of Laguesse, who understands under the pulmonary acinus the respiratory cavity, the system of alveolar passages, *with exclusion of any bronchial components*, has much in its favor.

One might well raise the question here: Why, if the designation "acinus" is conceived so differently by different workers, was no agreement reached upon another term, for example the "lung lobule," as described and presented by W. S. Miller in his various papers? The

FIG. 19

FIG. 20

FIG. 19. Microphotograph of a thin section 1.5 cm. below the pleura. Picture shows terminal branches of the bronchial tree containing a bronchiolus terminalis, two transitional bronchioles and the lung acinus proper.

FIG. 20. Microphotograph of a thin section about 2 cm. below the pleura. The same details as in fig. 19 can be seen.

reasons for rejecting Miller's "lung lobule" are to be sought, in part, in objections of anatomical nature against his description of the lung lobule, which his profuse nomenclature did not in any way help to advance, and partly on purely practical considerations. Even before Miller, various authors distinguished between, or rather mistook one for another: lung lobule, secondary lobule of the anatomists (Sappey), primitive lobule, lobuline of Grancher, infundibula of Rossignol, alveolar saccules, etc. According to the inclinations and requirements of the individual authors, the terms were used loosely and interchangeably. The designation "lobule," and, consequently, also the term "lobular" and "sublobular," were already in use for designating macroscopic units, which explains perhaps the disinclination to apply this term also to microscopic formations. Moreover, many pathological processes in the lung show a distribution and arrangement which has no relation to the gross lobule. For these reasons many authors adopted the designation "acinus," which seemed to put a stop to the chaotic confusion in the terminology of the terminal bronchial sections, and to be more useful for practical requirements.

In spite of the obvious differences in the width allotted to the concept *pulmonary acinus*, the various authors all conceive now under their pulmonary acinus the last morphological and functional unit of the lung parenchyma, and they are joined by W. S. Miller who claims the same thing for his lung lobule.

To our knowledge, Loeschcke is one of the few authors who paid special attention to the subdivision of the terminal branches of the bronchial tree by septa. We saw, however, above, that Loeschcke's acinus comprises two acini in Husten's sense. His acinus is, therefore, considerably greater than, and essentially different from what, in agreement with Laguesse, we like to have designated *acinus*. Of his acinus Loeschcke now says that it is generally but not invariably delimited from neighboring acini by septa (septa interacinaria), which produce the fine-patched aspect upon the lung surface. Only the thicker septa enveloping several fields, are septa interlobularia. Between the terminal sections of the two respiratory bronchioles, one never finds a septum formation, as Loeschcke points out emphatically. Delimited by septa interacinaria, his acinus, therefore, presents itself to Loeschcke as the terminal unit of the lung parenchyma. The acinus of Husten, Aschoff, and Loeschcke, as well as the lung lobule of W. S. Miller, which these authors regard as the terminal lung unit from the morphological and functional viewpoint,

have this in common, *that they are made up of various elements*: besides a certain amount of supporting substance, as found in any body tissue, they contain ciliated epithelium, high prismatic, cuboidal and, finally, so-called flat "respiratory epithelium." *To us, it seems, from the outset, inadmissible to designate as a morphological "unit" a formation composed of so many different elements.* Aschoff's comparison of the respiratory bronchioles to the "intercalated portions" (*Schaltstuecke*) of the alveolar passages, and of "alveolar saccules" to the secreting elements of the secreting glands, also cannot help us over these purely conceptual difficulties. *Of a morphological unit we must demand that it be composed only of morphologically alike elements.* This requirement is, however, in no way fulfilled by the morphological "units" of the above noted authors, be it a "lung lobule" of W. S. Miller, or an acinus of Husten, Aschoff or Loeschcke.

Now, as to the statement of Loeschcke, that beyond the terminal bronchiole whose ramifications compose his acinus, one never finds a septum, it is opposed to my own above-described and illustrated findings. We are able to show that the acinus, as we consider it, is enveloped by a very delicate septum interacinare. We were furthermore able to demonstrate that these delicate septa interacinaria each issue from the site of the transitional bronchiole where the cuboidal epithelium changes into the flat "respiratory epithelium" of the alveolar passages. It is also at this spot where the accompanying arteries subdivide. Beyond the point of issue of this septum, we find only flat "respiratory epithelium."

Thus, the terminal morphological and functional unit of the lung parenchyma, the lung acinus as conceived by Laguesse, is unequivocally and sharply outlined from the morphological viewpoint. It is composed of homogeneous elements, the so-called "respiratory epithelium" lining the walls of the alveolar passages and alveoli, *with the exclusion of any bronchial component.* It is a *functional unit*, since in the unit composed of but homogeneous elements, the ideal alveolization of the bronchial tree for the purpose of the gas-exchange, is attained. And this terminal unit is delimited from heterogeneous or neighboring structures by a distinct septum.

Definition of terms: If we intend, therefore, to apply the concept *acinus* to the architectural conditions of the lung, it seems to us, on the basis of the above-expounded criteria, the most adequate thing to comprise within the pulmonary acinus only the still further branching alveolar passages and their terminal sections, with the exclusion, however, of any

bronchial components. It is the terminal morphological and functional unit of the lung parenchyma. In view of the variable length of the "respiratory bronchioles," it may be left open either to distinguish several orders, *or to designate them generally as "transitional" bronchioles.* In opposition to Laguesse, I propose to maintain, for the time being, the designation "transitional bronchioli" of the first and second orders. The variability in these conditions of the terminal sections of the bronchial tree is, in fact, conditioned mainly by the space available to the pulmonary elements for their development.

My stand toward the presentation of W. S. Miller, I have already, in part, made clear above. As I have pointed out, Miller's conception distinguishes itself from that of all other workers in that, according to it, three to six round openings lead from the "ductulus alveolaris" into approximately spherical cavities, for which Miller introduced the designation "atria" into the literature. From those, further irregular cavities (air-saccules) would arise, which on their surface bear "air-cells" or alveoli. Against the description of Miller, already in 1902 v. Ebner pointed out that the newly distinguished sections possess no special histological characteristics, and that the profuse nomenclature might not help to make things clearer. J. Mueller denied the existence of "atria," whereas Justesen admits that, in cattle, "this cavity is a well developed element, deserving a name of its own." Justesen has not, however, any experience on human lungs and, consequently, does not give his opinion about it. E. Laguesse, to whom we owe the best and most precise reconstruction of the terminal sections of the bronchi, saw no "atrium" in human lungs, no more than did Husten, Loeschcke, or Ogawa. The latter worker supports his views likewise by reconstruction. According to Ogawa, Keil did not observe it in the lungs of sheep, whereas he admits its existence in that of dogs.

My own work, which represents the terminal endings of the bronchial tree in "ideal longitudinal sections," does not justify the distinction of an "atrium" in Miller's sense, least of all in those regions where Miller locates it, that is, between the transitional bronchioles and the alveolar passages. It may here be said also that Miller's picture in his *Harvey Lecture*, 1924, which is illustrated above (figure 5), is not very convincing for the existence of an "atrium" in that picture either. With Laguesse, I am, therefore, compelled to say: "Non, il n'y a absolument rien de tel. . . ." With respect to Miller's "lung lobule" as the terminal unit of the lung parenchyma, I refer to what I have said above.

8. SUMMARY

"Ideal longitudinal serial sections," that is, sections cut in the longitudinal plane of the terminal bronchial endings, show that in the human lung, *the terminal bronchiole, which* according to its structure and character *is a genuine bronchiole and bears no alveoli, divides dichotomously into two transitional bronchioles of the first order.* These contain, in their wall, besides the usual bronchial elements a few alveoli. The significance of these first alveoli for the gas interchange is, however, disputed, since, besides alveoli with so-called "respiratory epithelium," one encounters others to which any functional significance must be denied. *After a very short course, the transitional bronchioles of the first order, in their turn divide dichotomously into two transitional bronchioles of the second order.* But even with the presently increased number of alveoli in the walls, the functional significance of these yet remains questionable. *From the transitional bronchioles of the second order arise the "alveolar passages,"* the walls of which are composed solely of flat "respiratory epithelium," and of alveoli likewise built up of this epithelium. *The alveolar passages also divide dichotomously before breaking up into a system of narrower terminal alveolar ducts.*

The "system of alveolar ducts" emerging from the division of the alveolar passages, *with the exclusion of any bronchial components, is, in agreement with Laguesse, designated "pulmonary acinus." It is, morphologically and functionally, the terminal unit of the lung parenchyma,* since it is built up entirely of homogeneous elements, the so-called "respiratory epithelium," and since in it the complete and ideal alveolization of the bronchial tree is attained. It is delimited from neighboring structures, by a distinct septum interacinare. This morphological and functional unit is thus once more clearly and distinctly delimited. The units of other authors, be they designated "lung lobule" or likewise "pulmonary acinus," all fail to fulfill these strict requirements of the terminal morphological and functional unit, and are, therefore, to be rejected. In this entire canal system, there is nowhere to be seen an "atrium" in the sense of a well-defined cavity, such as described and introduced into the literature by W. S. Miller.

The architecture of the terminal sections of the bronchial tree, and, therefore, of the lung parenchyma, is quite simple and as follows: The *macroscopic unit* is the lung lobule, a somewhat pyramid-shaped formation, the basis of which measures about 10 to 12 sq. mm. At its tip

enters the intralobular bronchus which gives off several collaterals. After division in their turn, these collaterals very soon break up into the terminal ducts, or acini, lined by alveoli. Beyond the middle of the lobule, the intralobular bronchus begins to divide dichotomously into smaller bronchioles, of which there may be distinguished up to the eighth order. The last order to bear no alveoli is designated *terminal bronchiole*. After a short course, this terminal bronchiole divides into the transitional bronchioles, which bear alveoli in their walls and, as a rule, comprise two orders which follow one another at a very short distance. These transitional bronchioles (Laguesse) divide dichotomously into the alveolar passages, the walls of which are lined with alveoli all around, and these eventually subdivide into a canal system of narrower alveolar ducts, the pulmonary acinus proper. The pulmonary acinus is enveloped by a distinct septum, is built up of but one sort of epithelium, *and must be considered as the terminal unit of the lung parenchyma.*

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THE OPERATION OF PASCAL'S PRINCIPLE IN THE LUNGS AND PLEURAL CAVITIES[1]

EPHRAIM KOROL[2]

Pascal's law: Any pressure exerted on the surface of a fluid is transmitted throughout the fluid equally in all directions. Pressure applied to any point on the surface of a fluid is exerted at all points of the container of the fluid.

Both liquids and gases obey this law first enunciated by Pascal. The properties common to both gases and liquids which render them subject to this law are presumably the displacibility of their molecules upon each other and the relatively low internal friction of all fluids.

THE OPERATION OF PASCAL'S LAW IN PLEURAL EFFUSIONS

In the chest there is normally a thin layer of fluid separating the visceral from the parietal pleura. This fluid is too small in quantity to permit the play of the laws of hydrostatics. There are just enough fluid molecules to clothe the pleural surfaces by adhesion, so that during the respiratory movements the low internal friction of the fluid is substituted for the friction of the pleural membranes; there are not enough free molecules of the liquid to be displaced from point to point by the application of pressure to the chest; therefore, the pleural fluid in physiological quantities does not respond to gravity or to Pascal's Law. Pressure applied to the chest-wall is exerted on the lung immediately underlying, and is not transmitted through the pleural fluid to the entire visceral surface of the lung. Only after a sufficient increase in the amount of pleural fluid, as occurs in various pathological states, can Pascal's Law come into effect.

Under physiological conditions the different regions of the lungs do not expand and contract evenly in the two phases of respiration. The basal portions of the lungs adjoining the diaphragm and the long movable ribs

[1] Published by permission of the Medical Director of the Veterans' Administration who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

[2] Veterans' Administration, Lincoln, Nebraska.

have much greater respiratory activity than the apical and mediastinal portions of the lungs (1). The intrathoracic pressure is not equal in all regions of the chest but is lower in the more active regions and has values nearer atmospheric pressure in the apical and mediastinal regions (2) (3) (4). In pleural effusion, however, during the inspiratory enlargement of the chest, the pressure falls evenly at all points; during expiration the rise in intrapleural pressure is equally exerted on the entire lung surface in contact with the fluid. The action of the muscles of respiration is thus evenly translated to all portions of the lungs, so that in pleural effusion and pneumothorax there occurs an actuation of the apical and mediastinal regions of the lungs and a lessened ventilation of the basal region.

In figure 1, representing a case of pleurisy with effusion in the two phases of respiration, it can be easily seen that ventilation is much greater in the lung which is separated from the chest-wall by the effusion than in the opposite lung.

THE OPERATION OF PASCAL'S LAW IN PNEUMOTHORAX

In pleural effusion the increased ventilation of the partly collapsed lung can be observed only occasionally, as there are generally certain

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FIG. 1. Right-sided pleural effusion with pulmonary tuberculosis. The entire right lung appears veiled due to a thin layer of pleural fluid. X-ray observations made after aspiration of fluid and air replacement showed that the upper lobe was adherent, the middle and lower lobe partly collapsed.

A. Inspiration. B. Expiration, taken at the same sitting as A. Note the great collapse of the lower and middle lobes of the right lung as compared with the corresponding areas of the left lung.

FIG. 2. Case of bilateral artificial pneumothorax. The right upper lobe is fibrotic, the left upper is consolidated and has dropped downward and inward; only the right middle and lower lobes and the left lower lobe are air-bearing.

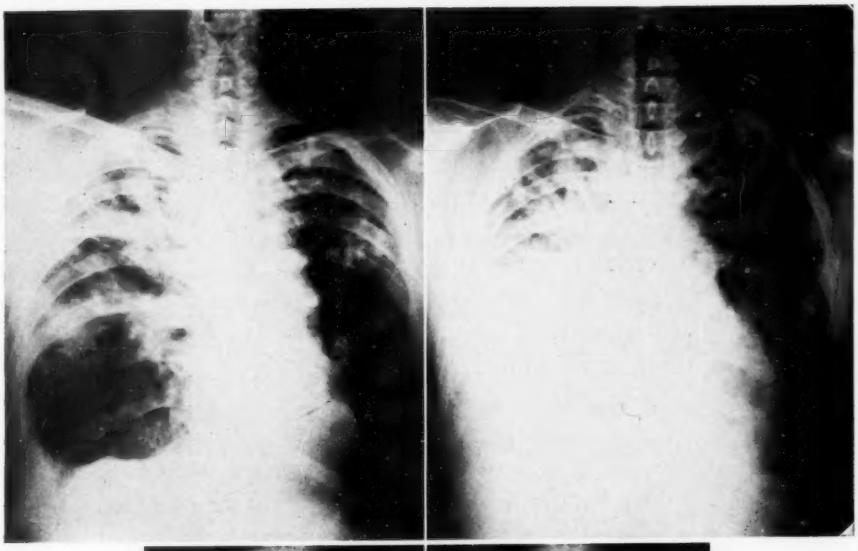
A. Inspiration. The lung is inflated and is in contact with the lateral chest wall on each side. B. Expiration, taken at same sitting as A. The lungs have collapsed more than the chest.

FIG. 3. Extensive fibrosis of right lung following pneumonia. Trachea and heart displaced to right.

A. The left lung has invaded the right hemithorax so that its anterior and posterior mediastinal borders can be seen to the right of the spine. The anterior border forms a pear-shaped hernia (outlined by arrows). The original film shows several round and oval emphysema blebs to occupy the region of the right upper lobe. B. Expiration, taken at same sitting as A. Note the migration and ventilation of the mediastinal regions of the left lung on each side of the spine. The lung hernia is no longer visible; the posterior mediastinum contracted to a lesser extent. The emphysematous upper lobe has enlarged and contains more air in expiration than in inspiration. The heart has moved to the left encroaching on the lung root region.

FIG. 1A

FIG. 1B



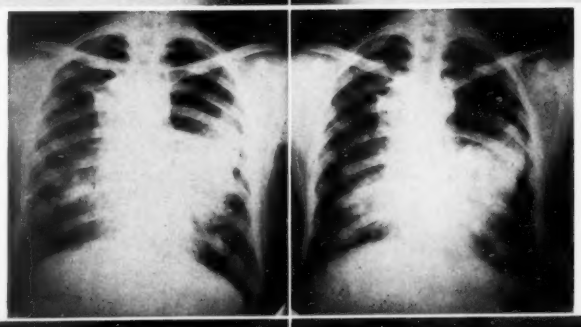


FIG. 2A

FIG. 2B

FIG. 3A

FIG. 3B

concomitant changes in the affected lung limiting its expansibility. These changes may consist of consolidation or fibrosis of the lung tissue; the visceral pleura may be stiffened, or the bronchi may be occluded by exudate or inflammation so that ventilation is impossible. In the cases of pneumothorax, on the contrary, more especially in artificial pneumothorax, the increased respiratory activity of the collapsed lung can be observed in all cases. It is curious that this phenomenon has not been previously discussed in the literature, although it is a matter of daily observation in the pneumothorax clinic.

Several writers have marvelled at the absence of dyspnoea in cases of extensive bilateral pneumothorax (5) (6) (7) (8). The observation has been repeatedly made that after the induction of pneumothorax the vital capacity does not diminish as much as might be expected (9) (10) (11). Upon reëxpansion of the lung following artificial pneumothorax the vital capacity has been observed to decrease (12). Pneumothorax treatment has been used for the relief of dyspnoea in massive atelectasis (13), in emphysema (14), in chronic bronchitis (15), and in lobar pneumonia (16) (17) (18).

Cutler (19) observed during fluoroscopic examination that the pneumothorax lung makes unexpectedly large respiratory excursion. Kuma (20) made similar observations in animal experiments. Several writers have presented X-ray photographs made of pneumothorax cases in inspiration and expiration (21) (22) (23). These pictures show in a startling manner the hyperfunction of the "collapsed" lung; the authors, however, do not comment on this phenomenon. Fleischner (24) seems to have recognized the exaggerated activity of the partly collapsed pneumothorax lung. Olmer and Raybaud (25), while making tracings of the movements of the chest-wall and of the collapsed lung in cases of pneumothorax, found that vigorous intrapleural movements may persist after the costal movements have become too feeble to register on the kymograph. These authors attributed the movements of the collapsed lung to the action of the contralateral lung transmitted to the collapsed lung by way of the mediastinum.

However, the exaggerated activity of the collapsed lung is observed also in cases of bilateral pneumothorax. (See figure 2.)

THE OPERATION OF PASCAL'S LAW IN EMPHYSEMA BLEBS AND IN TUBERCULOUS CAVITIES

The various regions of the chest-wall are not uniformly supplied with bone and muscle. In the posterior and lateral aspects of the chest the

ribs are close together and there are several muscle-layers; the upper and anterior intercostal spaces are rather wide and are relatively unprotected by muscle. The lung apices are particularly exposed, while there is no respiratory muscle about the mediastinal portions of the lung. The expiratory muscles (the abdominal muscles) are attached to the base of the chest, while the large inspiratory muscles (scalene, sternomastoid, etc.) are inserted in the upper part of the chest. During expiratory efforts made with closed or narrowed glottis (coughing, straining efforts, singing, etc.) air is driven from the basal portions of the lungs outward, but, as it cannot escape due to the closed glottis, the air under pressure evenly distends the alveoli in the regions which are unprotected by bone and muscle, namely, the apical and mediastinal portions of the lungs. For this reason pulmonary emphysema affects the apical and mediastinal portions of the lungs earlier and more extensively than other regions (26). As pointed out by Tendeloo (27) the barrel-shaped chest of emphysema is a product of the uniform distention which certain regions of the chest undergo during expiratory efforts.

Bullous emphysema: Large emphysema blebs are found associated with strictures of the supplying bronchi (28) (29) (30). These strictures act much like the glottis; that is, they admit air in inspiration but do not permit its escape in expiration. There is a tendency for these blebs to enlarge eccentrically with each expiration, particularly so in the regions of the chest deficient in musculature. On X-ray films these blebs appear spherical and larger in expiration than in inspiration. This expiratory enlargement has been demonstrated during postmortem examination: the blebs enlarge if the lung is compressed manually (31). (See figure 3.)

Tuberculous cavities: These cavities are also frequently associated with bronchial strictures. Their spherical shape is well known, and their tendency to eccentric enlargement. Elsewhere (32) we have shown illustrations of tuberculous cavities enlarging in expiration. Von Muralt also recognized the expiratory enlargement of tuberculous cavities (33).

THE TRANSMISSION OF PRESSURE THROUGH THE MEDIASTINUM

The mediastinum consists of several elastic tubes containing blood or air. Is it a solid or liquid structure? Characteristic of all liquids are the absence of any definite shape, an incompressibility and the ability to transmit pressure. The normally flexible mediastinum possesses these properties of a liquid. The shape of the mediastinum varies in the same individual during the respiratory phases, being long and

narrow in inspiration, short and broad in expiration; its shape and position also vary with the different bodily postures, with the varying positions of the diaphragm; also with the varying abdominal and gastro-intestinal contents. The normal mediastinum is sensitive to pressure changes in the one or the other pleural cavity, shifting readily to the side of the lessened pressure. In the cases in which pleural adhesions interfere with the production of artificial pneumothorax, the mediastinal region of the diseased lung may be compressed by inducing a pneumothorax on the opposite side (34) (35) (36). In all cases in which there is diminished ventilation of one lung, whether due to lung or pleural pathological processes, the mediastinum, unless fixed by adhesions, changes position with each respiratory movement. This pendulum movement of the mediastinum was recently discussed by Lenk (37). During inspiration, as the intrathoracic pressure sinks on the affected side the mediastinum moves toward this side; during expiration it moves to the opposite side. The respiratory fluctuations in pressure on the diseased side, as they are not neutralized by an exchange of air with the atmosphere, are transmitted to the mediastinal surface of the functioning lung, increasing the ventilation of this usually inert lung region. The lower and anterior region of the mediastinum (that is, the heart) being its most flexible part, this activation of the better lung principally affects its lower and anterior portions, namely the lower part of the upper (anterior) lobe. It is well known that the spread of infection from one lung into the other is favored by these mediastinal movements, and the site of the new infection is largely determined by these movements. Thus in artificial pneumothorax the dreaded appearance of lesions in the contralateral lung does not take place in the lung apex but in the lower portion of the upper lobe (38) (39). (See figure 3.)

SUMMARY AND CONCLUSIONS

1. Under normal conditions the several regions of the lungs vary in their respiratory efficiency, depending upon the activity of the overlying chest-wall; the movements of the lung are limited in extent by those of the chest. If the lung is separated from the chest-wall by a layer of fluid or gas, the movements of the chest-wall are exerted evenly on the entire lung, in accordance with the *Law of Pascal* governing the transmission of pressure in fluids. The collapsed lung, functioning without residual air shows greater respiratory excursions than the overlying chest-wall.

2. The localization of emphysema in the lungs, the spherical shape of emphysema blebs and of tuberculous cavities and their tendency to eccentric enlargement are attributable to the operation of *Pascal's Principle.*

3. The mediastinum transmits pressure like a fluid. In all cases of unequal expansion of the two lungs, the mediastinum transmits the respiratory fluctuations of intrathoracic pressure in such manner as to increase the ventilation of the better lung. The lower portion of the upper lobe is particularly affected. This is a factor in the reactivation of tuberculous lesions and in the interpulmonary spread of infection.

I am indebted to J. E. Almy, Professor of Experimental Physics, University of Nebraska, for a discussion and elucidation of the physical principles considered in this article.

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THE PRECIPITIN REACTION TO PHOSPHATIDES OF TUBERCLE AND LEPROSY BACILLI[1,2]

G. R. DUNCAN, C. C. VAN WINKLE, E. S. MARIETTE AND E. P. K. FENGER

The Research Committee of the National Tuberculosis Association assigned us the problem of standardizing the four phosphatides prepared by R. J. Anderson from the human, avian and bovine tubercle bacilli and leprosy bacillus for their antigenic properties in a quantitative precipitin test (1) (2) (3) (4).

Pinner had been successful in using the original human tubercle-bacillus phosphatide prepared by Anderson as antigen in complement-fixation tests (5). Using the same human tubercle-bacillus phosphatide as antigen, Doan reported the presence of a precipitin substance in human sera from cases of tuberculosis. With the bovine phosphatide as antigen he also demonstrated precipitins in the sera of cattle infected with bovine tuberculosis. He was able to produce specific antisera in rabbits when he used the human and bovine phosphatides as antigens. Using antiserum produced by the human phosphatide, he demonstrated an antigen which he concluded was free phosphatide in the sera of moribund cases of tuberculosis (6) (7) (8) (9) (10) (11) (12) (13).

The work of these two men made it seem desirable to work out a quantitative technique for the precipitin test. Our working hypothesis was that the phosphatide elaborated by the tubercle bacillus in the patient's body probably acted as an antigen and produced a specific antibody. If the amount of the tubercle-bacillus-phosphatide antibody could be measured in a differential manner, it might be possible to estimate the resistance of the patient and then possibly build up his antibody content artificially. Therefore, we had the problem of determining quantitatively the amount of antibody or antigen or both in patients' sera. In addition to this we were interested in the group relation if any, among the phosphatides from the four acid fast bacilli. This meant that we must set up the tests so that one phosphatide could be compared with all the others and cross-specificity tests be set up.

[1] Presented at a session of the Pathological Section of the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 30, 1933.

[2] From Glen Lake Sanatorium, Oak Terrace, Minnesota.

The general plan of the work was to take time to do each step of the theoretical and experimental laboratory work thoroughly and later to apply it to patients. We deliberately started with laboratory experiments, as the work with patients would be more interesting and the preliminary laboratory tests tedious. But when the human phosphatide proved so disappointing in the laboratory tests very little further work was done. A few tests with each phosphatide were run with patients' sera to check the laboratory work. The antisera on hand were cross-tested for specificity. Although it was felt that due to the method of their manufacture and the probable close relationship of the antigens to each other no crossing could be demonstrated, it did not seem worth while at that time to try to produce more comparable antisera.

We decided to use the Kahn test technique instead of the contact ring test that Doan had used (14). Each reagent could then be accurately measured and thoroughly mixed. We felt that this would give quantitative results and would be simpler to use than the complement-fixation technique. In order to use this technique, we had to find a diluent for the phosphatides and determine the concentrations of it necessary for use with each phosphatide. We also had to produce specific high-titre antisera for the cross-specificity tests and for demonstration of free antigen in patients' sera.

On February 6, 1932, we received from Anderson one sample each of human, avian, bovine and lepra phosphatides. On February 20, 1933, a year later, we received from Sharp and Dohme a second sample of human phosphatide. These constituted our antigens. The five phosphatides received were as follows:

5 gm. phosphatide from human tubercle bacilli H37 (S-1)
1 gm. phosphatide (A-3) from human tubercle bacilli H37 (S-2)
5 gm. phosphatide from bovine tubercle bacilli no. 523
5 gm. phosphatide from avian tubercle bacilli no. 531
3 gm. phosphatide from Bacillus leprae no. 370

The first sample of human phosphatide received will be referred to in this article as sample one (S-1). The second sample of human phosphatide will be referred to as sample two (S-2). According to Dr. Anderson, the history of human phosphatide (S-1) is as follows:

It was prepared from the composite lot of extract of H-37 obtained from the Mulford Laboratories. The cultures had been grown for varying periods of time and some of the extracts had stood for quite a long time before we obtained

possession of them. It is perhaps not surprising, therefore, that the phosphatide obtained from this material differs somewhat in properties from the original preparation made a few years ago. . . . In case you observe any differences in biological reaction from those mentioned by Pinner and Doan, the reason will probably be that it is due to the slight variation in composition which I have just described.

The second sample of human phosphatide (S-2) received from Dr. Reichel, Sharp and Dohme Laboratories, was originally made by Anderson. Dr. Anderson gives the following history of the second sample of human phosphatide: "The sample of phosphatide . . . was prepared in this Laboratory last year from an old alcohol-ether extract of H-37. . . . The preparation is not the original phosphatide used by Doan." The samples of bovine, avian and lepra phosphatide were the original lots prepared by Anderson. The bovine and avian phosphatides were the

TABLE 1

Amount of sediment present at 48 hours

PHOSPHATIDES	DISTILLED WATER	$\frac{N}{10}$ SOLUTIONS			
		NaCl	*NaBr*	$MgSO_4$	$CaCl_2$
S-1	−	−	−	−	++++
Bovine	−	−	+	++	++++
Avian	−	±	±	−	++++
Lepra	Trace	+	+	+++	++++

ones used by Doan. The sample of lepra phosphatide was used for the first time in precipitin tests.

The first problem in the use of these antigens was to find the proper diluent for them. We originally suspended the antigens in physiological salt solution but found that the bovine, avian and lepra phosphatides showed sediment when allowed to stand 48 hours which was the period of time of the test. For this reason, we tested each of the antigens in distilled water and in several different salts for suspendability. Throughout these tests a concentration of 1 mgm. to 1 cc. was used. Table 1 shows that even with distilled water slight sediment occurs with lepra phosphatide. Of the different salts tested, sodium chloride shows the least sediment of the group. We then tested sodium chloride at various concentrations to determine the greatest concentration of sodium chloride that would not cause sediment. These solutions are tabulated as decimal fractions of a normal solution. Physiological salt solution is approxi-

mately 0.15 N. The results appear in table 2. The avian phosphatide was not tested below 0.03 N for suspendability in sodium chloride. It shows no sediment in distilled water. The sediment with the avian and lepra phosphatides was very slight in the concentration used in the test. The most concentrated sodium-chloride solution in which the antigen was suspendable but which would not cause appreciable sediment in forty-eight hours was chosen for use in the tests as indicated in table 2. This was done in order to have each antigen as sensitive as possible and at as nearly similar precipitation points as possible, so that comparative figures on type-specificity could be made. No aqueous diluent satisfactory for all the phosphatides was found. The human types of phosphatide were the most suspendable and the avian and the lepra the least.

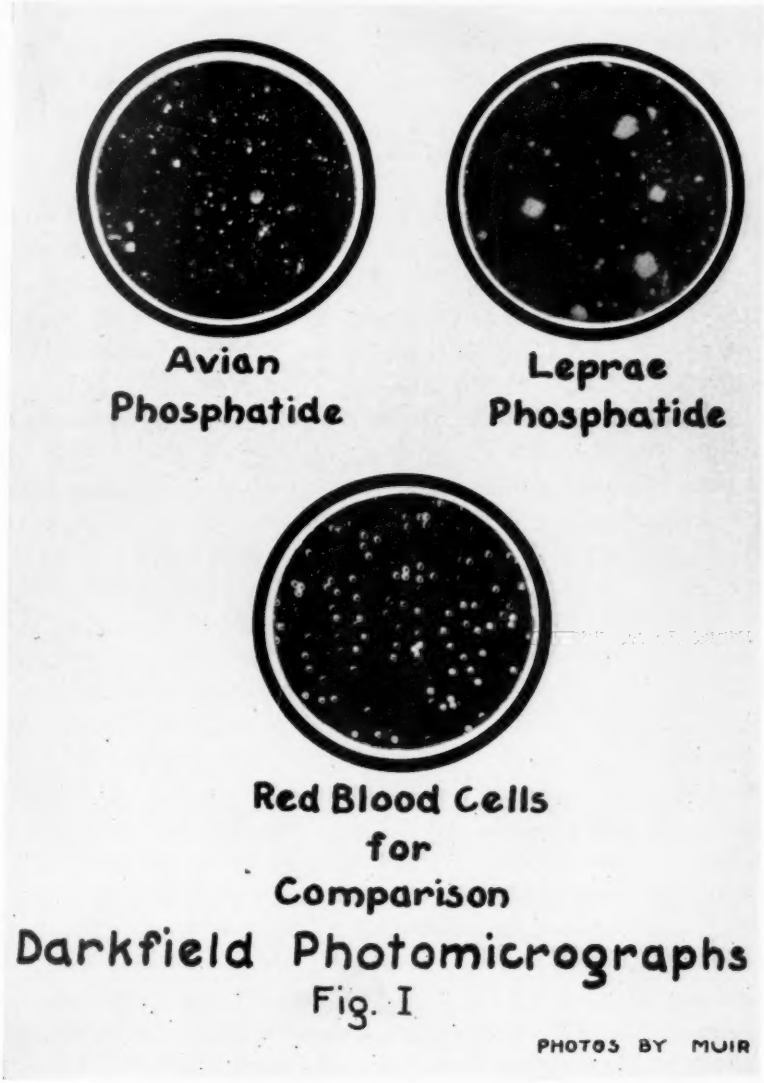
TABLE 2

Suspendability of various phosphatides in sodium-chloride solutions

PHOSPHATIDE ANTIGEN	CONCENTRATION OF SODIUM CHLORIDE CAUSING		CONCENTRATION USED IN SUBSEQUENT TESTS
	Slight sediment	No sediment	
S-1	0.5 N	0.4 N	0.4 N
S-2	0.18 N	0.16 N	0.15 N
Bovine	0.11 N	0.1 N	0.1 N
Avian	0.03 N	0.00 N	0.075 N
Lepra	0.00 N	—	0.01 N

The behavior of human (S-1) phosphatide as compared with the other phosphatides when suspended in sodium-chloride solution suggested the possibility of a different morphology for this antigen. Therefore, dark-field observations of the various phosphatides were made. The dark-field examination of the suspensions in sodium chloride shows similar morphology for the bovine, avian, lepra and human (S-2) phosphatides but a different one for the human (S-1). The suspensions of the former have the appearance of an emulsified lipoid showing mobile oil droplets and denser particles. In contrast to this the human (S-1) phosphatide shows merely tiny particles. The photomicrographs (figure 1) show two of the lipoid emulsions, avian and lepra, and red blood cells, the last taken at the same magnification for a standard of comparative size. We did not succeed in photographing human (S-1) phosphatide. The large masses of lepra phosphatide on vigorous shaking are broken up

and show a picture similar to the avian phosphatide. The larger masses indicate the difficulty encountered in making a suspension of this phos-



phatide. The bovine, avian and lepra phosphatides show the same appearance of emulsified lipoid when suspended in sodium bromide and magnesium sulphate. Human (S-1) phosphatide shows only the tiny

particles when suspended in these salts. Human (S-1), bovine, avian and lepra phosphatides all show immediate precipitation with calcium chloride. Human (S-2) phosphatide was tested with distilled water and sodium chloride only, as by the time it arrived we had definitely decided to use sodium chloride in the tests.

In the meantime normal healthy rabbits were inoculated with the phosphatides in order to produce a specific antiserum. Each rabbit had previously been tested for free antigen against patient serum and for free antibody with homologous phosphatide before being used. None of these tests were positive. We did not test with tuberculin as we felt this might influence the formation of antibodies. The animals all appeared healthy and had been isolated and observed for at least ten days before being used. Distilled-water suspensions of the phosphatides were used for the intravenous injections because the bovine, avian and lepra phosphatides could not be suspended in physiological salt solution. The dose of phosphatide was 2 to 3 mgm. per kg. Five injections at three-day intervals were given in each course, and several courses of injections were usually necessary before the precipitin titre was high enough for the animal to be bled to death. The rabbits had a rest period of approximately one month between the courses of injections. At the beginning of subsequent courses, 1 mgm. of phosphatide was given intravenously as the first injection, regardless of the size of the animal. After we had had several deaths from shock, 0.1 cc. of adrenalin was given intramuscularly at the time a new course was started. Adrenalin was not used with the injections of human (S-2). The temperatures were taken on all rabbits every hour immediately following the injections until they approached normal, and otherwise three times a day. Figure 2 shows typical temperature charts for the five phosphatides. These charts indicate that all five induce fever in rabbits when injected intravenously. Test-bleedings were made on the tenth day after completion of each course of injections and, if the precipitin titre was deemed satisfactory, the animal was bled to death on the twelfth day. All sera were filtered through Berkefeld or Seitz filters and merthiolate[3] (1–5000) was added as preservative. All rabbits were autopsied after the bleeding and

[3] One antiserum for each phosphatide was tested with and without merthiolate without showing any differences in reaction. Merthiolate was used throughout as a preservative for all the antisera. No deterioration was noted with bovine, avian and lepra antisera over nine to eleven months of observation. Human (S-2) antiserum showed no deterioration in the one month of observation.

microscopic sections studied for tubercles or epithelioid reaction. None showed tubercles. No definite evidence of epithelioid reaction could be made out in the sections stained with haematoxylin and eosin.

Table 3 shows the results of the series of inoculations of each phosphatide. In the end we had 7 antisera with which to carry out our

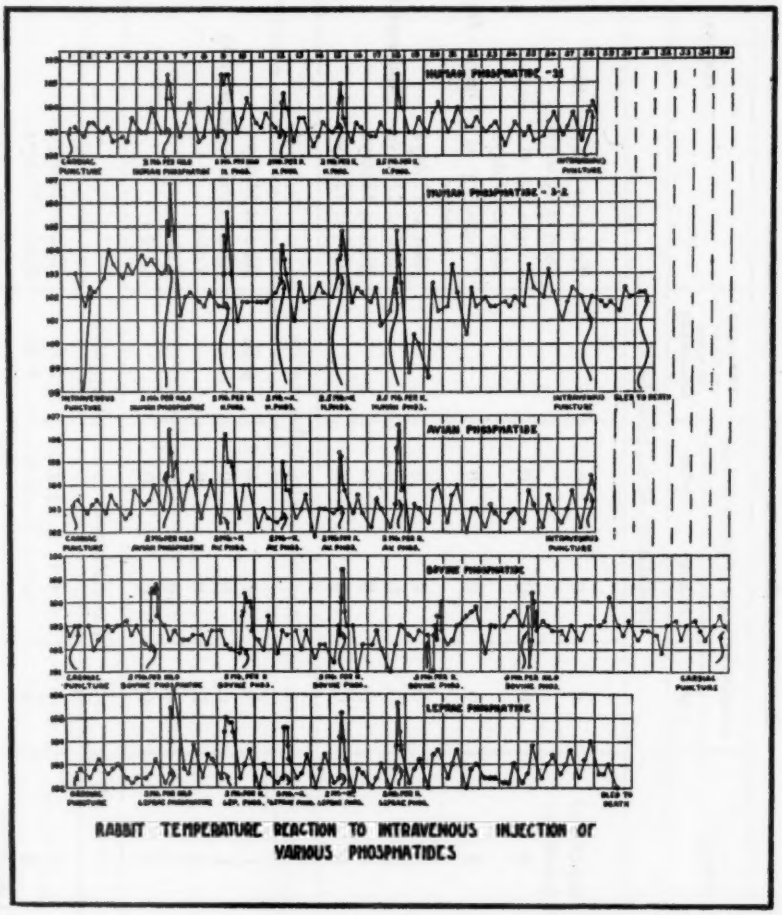


FIG. 2

tests. The avian and lepra phosphatides produced good antibodies in from one to three courses of injections. We had two sera each from these phosphatides. The bovine phosphatide took three to four courses to produce good antibodies and we had two satisfactory antisera from this phosphatide. In contrast to these the human phosphatides were

TABLE 3

Rabbit inoculations for the production of specific antisera

RABBIT NUMBER	DOSES	COURSES	ANTIBODY RESPONSE AT END OF COURSES			END POINT READ AT 48-HOUR MILLIGRAMS	REMARKS
			2-hour	24-hour	48-hour		
Inoculations of S-1 phosphatide							
	mgm./kg.						
1	1–2	(2 injections)	0	0	0		Tested at 7 days. Bled
2	1–3	(4 injections)					Died early of shock
3	2–3	3	0	0	0		2 mgm./kg. at 15 days Bled at 27 days
4*	2–5	3	0	0	0		2 mgm./kg. at 19 days. Intradermal tuberculin negative
5	2–2.5	3	0	0	0		Bled at 12 days
6	2–2.5	3	0	0	0		Bled at 12 days. (Abdominal tumor)
7	2–3.5	3	0	0	0		Bled at 12 days
8	2–3.5	3	0	0	0		Bled at 12 days
Inoculations of S-2 phosphatide							
1	2–2.5	1	+	+	+	0.01	Bled at 13 days
2	2	1	0	0	0		Killed (abdominal worms)
3	2–3	3	0	0	0		Killed
4	2–3	3	0	0	0		Killed
5	2–3	3	0	0	0		Killed
Inoculations of bovine phosphatide							
1	2–3	3	+++	+++	+++	0.01	Bled at 12 days
2	2–3	4	+	++	++	0.01	Bled at 12 days
3	2–3	(3 injections)					Died with thrombosis
4	2–3	(2 injections)					Died with cardiac thrombosis

			Inoculations of avian phosphatide				
1	2–3	1 + (3 injections)	0	+	+		Died early of shock
2	2–3	3	+++	+++	+++	0.01	Bled at 12 days
3	2–3	1 + (2 injections)	0	±	+		Died early of shock
4	2–3	2	+++	++++	++++	0.05	Bled at 12 days
			Inoculations of lepra phosphatide				
1	2–3	2	+++	+++	+++	0.01	Bled at 12 days
2	2–3	1	++++	++++	++++	0.01	Bled at 12 days

* Test-bleedings after completion of 1st course at 2nd, 4th, 7th and 10th days. No precipitin response at any time.

unsatisfactory and very disappointing. The human (S-1) phosphatide never produced precipitin antibodies even when the rabbits received three courses of injections and as much as 5 mgm. per kg. The human (S-2) phosphatide gave a one-plus reaction in one animal at the end of a single course of injections. This animal was bled to death at that time so that we could do some of the preliminary tests, but none of the other animals produced antibodies with this phosphatide, even when carried through three courses. We had only one antiserum from the human phosphatide and that a weak one. Thus no satisfactory antiserum was produced from the human phosphatides (S-1) and (S-2). The other three phosphatides produced satisfactory antisera.

With the diluent for the phosphatides decided upon and the antisera on hand we were ready to set up the tests. The volume of each of the two reagents used was made up to 0.5 cc., so that the total volume for the tubes of the mixture of antigen and antiserum was 1 cc. Gravimetric dilutions were used for the antigen, making it possible to record the results of the test as decimal fractions of milligrams. The greatest concentration of antigen used was 1 mgm. in 1 cc. This is the upper limit of suspendability of avian and lepra phosphatides. Further dilutions were made up to read in milligrams as follows: 0.5, 0.2, 0.1, 0.05, 0.02, 0.01, etc. This is the progression used when testing the end-point of the reaction. Closer-spaced dilutions were made to test the peak of the zone. In this case, the progression in milligrams was as follows: 1.0, 0.9, 0.8, 0.7, 0.6,—0.1, 0.08, 0.06,—0.02. The antiserum was diluted 1:10 which gave a final dilution of 1:20. Other dilutions from 1:5 to 1:40 of antisera were used when testing for the optimal proportions as described by Dean and Webb (15) (16). The diluent used for both phosphatide and antiserum was always sodium chloride in distilled water in strengths compatible with the suspendability of the antigen as shown in table 2. The series of tubes were then agitated for five minutes in a machine with a cycle similar to that of a Kahn agitator (14). Readings were made immediately after agitation and at short intervals for two hours at room temperature. Further readings were made at 24 and 48 hours from ice-box incubation. A control for phosphatide suspension and antiserum was included in each test. The most concentrated suspension of phosphatide was used as the control.

The 48-hour end-point of each of the 7 antisera in 1:20 dilution was determined when tested against its homologous phosphatide (table 3). The human (S-2), bovine, lepra and one of the avian antisera react with

their respective homolgous phosphatides out to 0.01 mgm. The second avian serum reacts out to 0.05 mgm. with its phosphatide.

Each phosphatide shows a characteristic manner of reaction with its homologous antisera. The human (S-2) phosphatide shows a slow and weak reaction. This becomes heavier as time elapses and the zone widens until at 2 hours there is flocculation in the tubes from 0.4 to 0.04 mgm. (table 4). The reaction starts earlier in the case of the two bovine sera and is heavier than the human throughout, but nevertheless it is relatively weak and slow. Both avian antisera give an immediate heavy reaction throughout a wide zone. The lepra antisera react more slowly than the avian, but flocculate earlier.

None of the sera are very potent. No attempt was made to reach the end-point in precipitin production in any of the animals. As soon as precipitins of moderate degree were produced, the serum was collected for tests. We were at that time only interested in standardizing the test.

In order to test the sera to see whether they followed Dean and Webb's rule of optimal proportions and also to determine the range of the reacting zone, we set up tests to read the peak tube in a series of antiserum dilutions. Dean and Webb's rule of optimal proportion is that, as the antigen is increased in concentration, the antiserum changes in concentration, so that the peak tube of each series maintains the same proportional relation of antigen to antiserum. However our values of antigen and antiserum for a given phosphatide do not show any such constant proportion (table 5). When these tests were set up, the antiserum for human (S-2) phosphatide was fresh, while the others were 8 to 10 months old. We were using a solid and a liquid rather than two liquids, which may account for the reactions found.

Since (S-1) phosphatide did not react with its presumably specific rabbit antiserum it was tested with 13 human sera from positive-sputum cases in 1:20 dilutions. It did not react with any of these. The (S-2) phosphatide was tested with 9 human sera from positive-sputum cases. None of these reacted. Four of these sera were then tested with bovine, avian and lepra phosphatide. Table 6 shows that the lepra phosphatide reacts the best of all the phosphatides in the presence of the human serum.

We thought that the failure of human (S-1) and (S-2) phosphatides to react with patient's serum or to produce satisfactory antibodies in the rabbit might be overcome in the test by changing the pH of the test-

TABLE 4

Tests selected to show zone and two-hour end-point for each phosphatide with its homologous antisera

TIME OF READING	MILLIGRAMS OF ANTIGEN														
	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.08	0.06	0.05	0.04	0.01	0.005	0.001
Human S-2															
Start					0	0	0	0	0	0		0	0	0	0
½ hour					0	0	0	0	0	0		0	0	0	0
1 hour					0	0	0	0	0	0		0	0	0	0
1½ hour					0	±	+	+	±	±		±	0	0	0
2 hours					±	++	++	++	++	+		+	0	0	0
Bovine serum 1															
Start					0	0	0	0	0	0			0	0	0
½ hour					0	±	+	±	±	±			0	0	0
1 hour					+	++	++	++	+	+			±	0	0
1½ hour					+	++	++	++	++	+			+	0	0
2 hours					+	+++	+++	+++	++	+			+	0	0
Bovine serum 2															
Start					0	0	0	0	0	0		0	0	0	0
½ hour					0	0	0	+	+	+		±	0	0	0
1 hour					0	+	+	+	+	++		+	0	0	0
1½ hour					+	++	++	++	++	++		++	±	0	0
2 hours					+	++	++	++	++	++		++	±	0	0
Avian serum 2															
Start					0	+	+	+	+	+		+	±	0	0
½ hour					+	++	++	++	++	++		+	±	0	0
1 hour					++	++	+++	+++	++	++		++	+	0	0
1½ hour					++	++	+++	+++	+++	++		++	+	0	0
2 hours					++	++	+++	+++	+++	++		++	+	0	0

Avian serum 4

Start	+	+	+	**++**	**++**	**++**	**++**	++			±		0	0	0
½ hour	+++	+++	+++	**++++**	**++++**	**++++**	**+++**	**+++**			+		0	0	0
1 hour	+++	+++	**++++**	**++++**	**++++**	**++++**	+++	+++			++		0	0	0
1½ hour	++++	++++	**++++**	**++++**	**++++**	**++++**	+++	+++			++		0	0	0
2 hours	**++++**	**++++**	**++++**	**++++**	**++++**	**++++**	+++	+++			++		0	0	0

Lepra serum 1

Start					0	±	**+**	+	±	±		±	0	0	0
½ hour					+++	**+++**	**+++**	++	++	+		+	0	0	0
1 hour					+++	+++	**+++**	++	++	++		+	0	0	0
1½ hour					+++	+++	**++++**	+++	+++	+++		+	0	0	0
2 hours					+++	+++	**++++**	+++	+++	+++		+	0	0	0

Lepra serum 2

Start	0	0	0	0	0	0		0			0		0	0	0
½ hour	+	+	+	**++**	++	++		+			0		0	0	0
1 hour	++	++	++	**++**	**++**	**++**		+			0		0	0	0
1½ hour	++	++	**+++**	**+++**	++	++		+			0		0	0	0
2 hours	++	++	**+++**	**+++**	++	++		++			+		0	0	0

Best reactions are in heavy type.

TABLE 5

Ratio of antigen and homologous antiserum in the peak tube

PHOSPHATIDE	CONCENTRATION IN MILLIGRAMS		RATIO OF ANTIGEN TO ANTISERUM
	Antigen	Antiserum	
Human S-2	0.1	0.2	1:2
	0.2	0.1	2:1
	0.3	0.05	6:1
Bovine:			
Number 1	0.2	0.1	2:1
	0.2	0.05	4:1
	0.4	0.025	16:1
Number 2	0.04	0.1	2:5
	0.06	0.05	6:5
Avian:			
Number 2	0.2	0.1	2:1
	0.2	0.05	4:1
	0.3	0.025	12:1
Number 4	0.3	0.2	3:2
	0.4	0.05	8:1
	0.6	0.033	18:1
Lepra:			
Number 1	0.2	0.1	2:1
	0.2	0.05	4:1
	0.3	0.025	12:1
Number 2	0.4	0.1	4:1
	0.4	0.05	8:1
	0.4	0.033	12:1

TABLE 6

Precipitin test of serum of four human cases of pulmonary tuberculosis and the four phosphatides

READ AT 24 HOURS			
Human S-2	Bovine	Avian	Lepra
0	+	+	+++
0	+	+	+++
0	+	?	+++
0	Slight	?	+++

mixture. Tests were made, using phosphatide (S-1) with normal human serum, serum from tuberculous patients and sera from rabbits 5, 7, and 8 of table 3 at pH 7, 6, 5 and 4. Two of the rabbit sera showed weak and slow reactions at pH 4 and 5. This shows that some specific change has taken place in the rabbit serum, but it is weak and not adapted to the test which we were using. None of the others reacted.

Realizing that the antisera which we had were inadequate, both in quality and numbers, and that the antigens were weak, we set up cross-specificity tests. We were not surprised to find that no specificity could be demonstrated. The lepra phosphatide, which is the strongest antigen and easily produces antibodies, dominated the tests. It reacted well with its homologous serum but equally well with all the other antisera. The phosphatides appear to be too closely related and too poor as antigens to easily demonstrate any specificity.

From our work with these antigens it seems possible that either the tubercle-bacillus phosphatide complex is unstable, so that fresh cultures must be used in its preparation, or that the reactions reported by Pinner and Doan are due to an associated substance which is lost or separated out very readily when old cultures are used.

CONCLUSIONS

1. Human phosphatide (S-1) does not act as an antigen for the production of antibodies in the rabbit.
2. Human phosphatide (S-2) acts as a very poor antigen for the production of antibodies in the rabbit.
3. Bovine, avian, and lepra phosphatides act as good antigens for the production of antibodies in rabbits.
4. Neither human (S-1) nor (S-2) phosphatides react with patients' sera in the tests as we have set them up.
5. Bovine, avian and lepra phosphatides all react with patients' sera.
6. No type specificity among the four phosphatides was demonstrated.
7. The sera do no follow Dean and Webb's rule of optimal proportions.
8. Dark-field examination shows bovine, avian, lepra and human (S-2) phosphatides to have a similar morphology. Human (S-1) phosphatide shows a different morphology.
9. Bovine, avian and lepra phosphatides are not suspendable in physiological salt solution. Human (S-1) and (S-2) phosphatides are suspendable in this concentration of sodium chloride.

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THE LESIONS IN RABBITS FOLLOWING INOCULATION WITH BACILLUS CALMETTE-GUÉRIN (*BCG*)

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Whether the *Bacillus Calmette-Guérin* is definitely and permanently innocuous is still a matter of controversy. Many investigators claim to have observed a restoration of virulence of the organism as a consequence of environmental influences exerted during artificial cultivation, whereas others are just as emphatic that the bacterium remains avirulent regardless of its environment. The observations to be reported at this time are concerned with the results of inoculation of rabbits with glycerin-broth cultures of the organism, the original strain of which was obtained from Calmette in January, 1930.

METHODS AND RESULTS

The organism: The culture, as received from Calmette, was growing on glycerin-broth-potato medium and was continued on similar media by subculturing at monthly intervals for nine months. It was then subcultured monthly on a medium composed of egg-yolk and 6 per cent glycerinated water. Twenty months later portions of the twentieth generation of the glycerine-egg-yolk culture were used to inoculate two flasks containing a glycerine-beef, broth-peptone medium.[2] Before inoculation the medium in one of the flasks was enriched by the addition of 10 per cent fresh horse-serum. Incubation was continued at 37.5°C. for sixty-seven days. At this time, in the flask to which the horse-serum had been added, there was a luxuriant growth of bacteria on the surface of the medium and at the bottom of the flask, while the intervening fluid remained clear. The flask that did not contain serum revealed a coarsely granular type of growth which remained at the bottom of the fluid. There was no surface growth.

Comparable portions of the bacteria, and of the fluid in which they had grown, were obtained from each flask and were placed on a mechanical

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[2] The medium contained the following: infusion from one pound of ground beef, 930 cc.; Bactopeptone, 10 gm.; glycerin, c. p., 70 cc.; monobasic potassium phosphate, 5 gm. The pH was not adjusted.

shaker for one hour. The resultant suspensions had a turbidity slightly in excess of that of tube 10 of the McFarland nephelometer. This was used to inoculate animals.

Transfers were made also from the growths occurring in the original flasks, and subcultures eventually were obtained.

Inoculations of animals: Each of the prepared bacterial suspensions was used to inoculate 3 rabbits and 3 guinea pigs. The pertinent data pertaining to this phase of the experiment are summarized in table 1.

Five of the rabbits lived for the duration of the experiment and were killed 174 days subsequent to inoculation. One of the rabbits died ten days following the injection. All of the rabbits that were killed on the one hundred and seventy-fourth day had strikingly significant, pulmonary, focal lesions (figures 1 and 2). Direct smears prepared from crushed lesions of the respective sets of lungs revealed acid-fast bacillary forms in variable numbers. Portions of the morbid pulmonary tissue of each rabbit were emulsified, and cultures were attempted after treatment with 5 per cent oxalic acid; results were negative. The same emulsions were used to inoculate a second series of 10 guinea pigs and 4 rabbits. This part of the experiment is summarized in table 2.

Although in the lungs of five of the rabbits that received inoculation with the broth cultures of *Bacillus Calmette-Guérin* there were marked and extensive tubercle-like lesions, and the presence of acid-fast bacteria was demonstrated in each by direct smear, inoculation of a second series of animals with material from these rabbits failed to produce lesions, and one must therefore conclude that the organisms present in the tubercle-like lesions at the time of death of the animals were avirulent.

At the time the animals of the first group were inoculated, a subculture of the growth in the flask containing the glycerin-peptone-beef broth medium, to which had been added the horse-serum, was made into another flask containing a medium of similar composition. At the expiration of 195 days an extremely luxuriant growth had occurred on the surface of the medium and portions were used to inoculate a third series of animals. The inoculum here also had a turbidity of approximately tube 10 of the McFarland nephelometer. The animals included 4 rabbits and 4 guinea pigs.

The fact that three of the rabbits in the last experiment died fifty-two days after inoculation depreciated somewhat the value of the results obtained in this portion of the study. Although it is true that ill-defined, tubercle-like lesions were obtained in the lungs of two of the rabbits, lesions comparable to those that occurred in the lungs of the rabbits in

TABLE 1

Rabbits and guinea pigs inoculated with sixty-seven-day-old broth culture of Bacillus Calmette-Guérin

ANIMAL	INOCULUM*	DAYS AFTER INOCULATION		RESULTS
		Killed	Died	
Rabbit 1.....	Broth culture, no serum	174		Moderate number of focal nodules throughout both lungs. Histologically, lesions were tubercles containing acid-fast bacteria†
Rabbit 2.....	Broth culture, no serum	174		Few scattered focal nodules in both lungs. Histologically, lesions were well established tubercles containing many acid-fast bacteria†
Rabbit 3.....	Broth culture, no serum	174		Innumerable focal lesions in both lungs. Tubercles were well-defined histologically and contained† acid-fast bacilli
Rabbit 4.....	Broth culture, horse-serum		10	Fibrinous peritonitis. Histologically, early tubercles were forming in lungs
Rabbit 5.....	Broth culture, horse-serum	174		Innumerable large nodules in both lungs. Histologically, lesions were proliferative and tubercle-like with a few acid-fast bacteria present†
Rabbit 6.....	Broth culture, horse-serum	174		Numerous nodules in both lungs. Histologically, numerous small tubercles containing acid-fast bacteria were present†
Guinea pig 1.....	Broth culture, no serum		57	Tuberculin sensitivity +3 at thirty-seventh day. No lesions were found at necropsy
Guinea pig 2.....	Broth culture, no serum		17	No tuberculous lesions were found
Guinea pig 3.....	Broth culture, horse-serum	145		Tuberculin sensitivity +3 at thirty-seventh day. No tuberculous lesions were found
Guinea pig 4.....	Broth culture, horse-serum	145		Tuberculin sensitivity +2 at thirty-seventh day. No tuberculous lesions were found

* Rabbits received intravenous injections; guinea pigs, subcutaneous injections. Each animal received 0.5 cc.

† Cultures attempted from emulsified pulmonary lesions were negative for acid-fast bacteria.

the first series did not develop. However, three of the four guinea pigs in this last series lived from seven to eight weeks and were without significant lesions at the time of death.

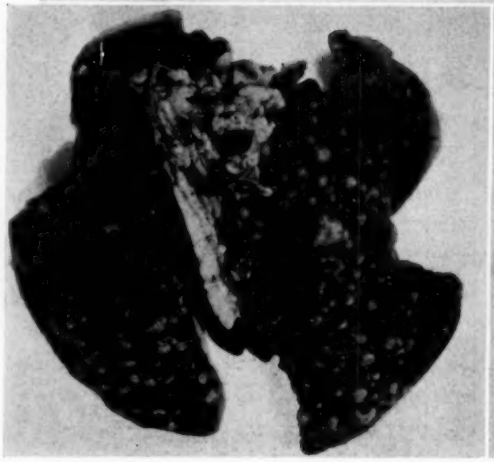
Pathology: The morbid changes observed in the rabbits, and recorded

in table 1, were restricted to the lungs. Although a microscopic study was made of the liver, spleen, and kidneys, in these organs no pathological changes were observed that could have been related to the bacterial inoculum.

FIG. 1*a*

FIG. 1*b*

FIG. 2*a*



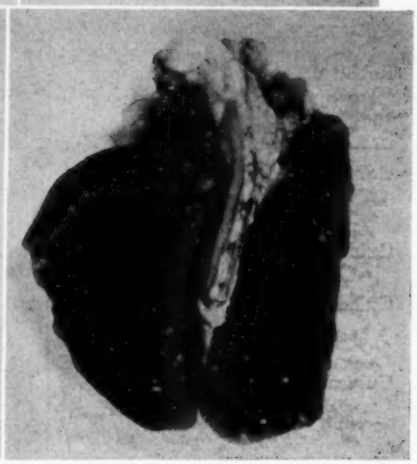


FIG. 2*b*

FIG. 1. *a*, Lungs of rabbit 1. *b*, Lung of rabbit 3. Animals killed 174 days after intravenous inoculation with beef-infusion-peptone-broth culture of *Bacillus Calmette-Guérin*.

FIG. 2. *a*, Lungs of rabbit 5. Focal tubercle-like lesions are particularly numerous. *b*, Lungs of rabbit 6. Both animals were killed 174 days after intravenous inoculation of horse-serum-beef-infusion-peptone-broth culture of *Bacillus Calmette-Guérin*.

Grossly, the lesions were strikingly evident to the unaided eye, and, although the extent or degree of morbid alteration varied somewhat in

respective sets of lungs, the lesions were pronounced in all of them. The majority of the focal lesions were from 0.2 to 0.3 cm. in diameter and were most numerous near the periphery of the lung, where they appeared as slightly elevated nodules, some of which were confluent. They were slightly yellow.

Involvement of the lymph nodes of the lungs was not apparent.

Microscopically, lesions in various stages of development and of retrogression were present. Those in the lungs of the rabbit that died ten

TABLE 2

Inoculation of animals with emulsified pulmonary tissue containing tubercle-like lesions obtained from rabbits 1 to 6 (table 1)

ANIMAL	INOCULUM*	DAYS AFTER INOCULATION		TUBERCULIN SENSITIVITY	RESULTS
	Pulmonary tissue of rabbit	Killed	Died		
Guinea pig 5	2	113		Negative	No lesions
Guinea pig 6	2		19	Not determined	Failure†
Guinea pig 7	1		13	Not determined	Failure
Guinea pig 8	1	113		Positive +2	No lesions
Guinea pig 9	3		157	Negative (1 test)	No lesions
Guinea pig 10	3	113		Negative (3 tests)	No lesions
Guinea pig 11	6	113		Negative	No lesions
Guinea pig 12	6		58	Negative	No lesions
Guinea pig 13	5		81	Negative	No lesions
Guinea pig 14	5	113		Positive +2	No lesions
Rabbit 7	5	112		Not determined	No lesions
Rabbit 8	5	112		Not determined	No lesions
Rabbit 9	5	145		Not determined	No lesions
Rabbit 10	5		143	Not determined	No lesions

* Rabbits received intravenous injections; guinea pigs, subcutaneous injections.

† Animals dying within twenty-one days after inoculation were considered "failures."

days after receiving the inoculum were composed largely of epithelioid cells and a considerable number of lymphocytes near the periphery, although a few cells of this character were distributed throughout the entire lesion. Polymorphonuclear leucocytes were not seen. In the smaller or earlier lesions in the lung of this same rabbit an occasional giant cell of the Langhans type was observed, but these structures were missing in the larger cellular accumulations. The majority of the lesions in this animal seemed to have a significant relationship to the blood-vessels and apparently had their inception in perivascular tissue. When appro-

priately stained, enormous numbers of acid-fast bacillary forms were evident in the centres of many of the lesions. These bacillary forms were arranged as dense irregular clusters or masses and were peculiarly restricted to the centre of the lesion, since individual bacteria were not found among cellular elements. There was no appreciable peripheral encapsulation.

The lesions in those rabbits that were permitted to live for 174 days after receiving bacterial inoculations were characterized by certain features of chronicity; outstanding among them was the tremendous lymphocytic infiltration surrounding the respective focal units. The lymphocytic elements were disposed in a rather wide zone which separated the lesions proper from the parenchyma of the lung (figures 3 & 4). The lymphoid cells also infiltrated irregularly among the peripheral epithelioid cells of the lesion. Necrosis was a prominent feature of most of the lesions in the 5 rabbits that were studied at necropsy 174 days after inoculation. The necrobiosis was usually caseous and frequently was so extensive that it involved practically all of the epithelioid elements of the lesion. In some instances the centres of the lesions had undergone softening, and the remains of a homogeneous substance could be seen. This change was most often observed among the larger lesions. Imperfectly formed Langhans giant cells occasionally were present and, in some of the lesions, a gradual transformation of the more or less irregularly spherical epithelioid cells into flattened, elongated, fibroblastic elements was suggested.

A study was made of the finer structural details of the epithelioid reactions in material stained by Pap's method for the demonstration of reticulum. This delicate fibrillar substance was found in abundance in all tubercle-like lesions except in those in which necrosis was advanced. The thread-like fibrils were very irregularly disposed, running in all directions and incompletely separating the epithelioid cells into small packets (figure 5). The reticulum content and its arrangement was not unlike that observed in the lesions of genuine tuberculosis in different species.

Acid-fast bacilli were present in the cellular detritus of practically all of the lesions, but in no instance was there mass accumulation of bacteria, such as occurred in the lesions of the rabbit that died ten days after injection. A minimal amount of mineral salts was detected in the necrotic tissue in a few of the lesions. Definite fibrous encapsulation, separating the lesions from the rest of the lung, never was seen. The

FIG. 3

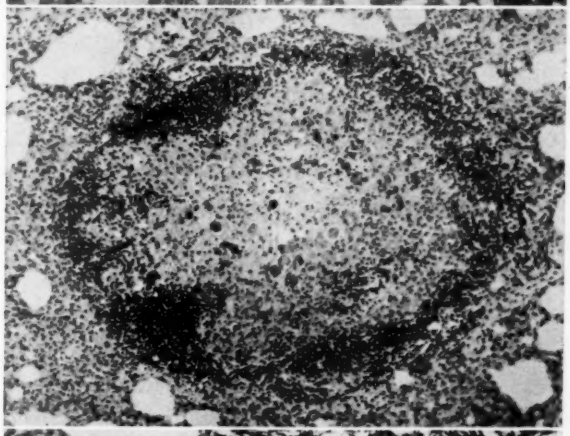


FIG. 4

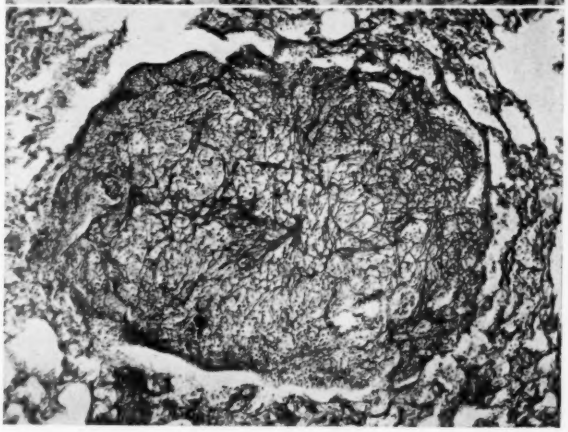


FIG. 5

FIG. 3. Lesions in lung of rabbit 6. Pronounced necrosis in one lesion. The structure of the other lesion is intact. (× 44.)

FIG. 4. Focal lesion in the lung of rabbit 6 killed 174 days after intravenous inoculation. Areas of necrosis in central portion of the epithelioid accumulation. Peripheral zone is composed largely of lymphocytes. (× 100.)

FIG. 5. Solitary tubercle-like nodule of the lung of rabbit 3. (Stained by Pap's method to demonstrate the reticular fibrils of the structure.) (× 100.)

lesions were frequently surrounded by a zone of more or less chronic pneumonitis.

All in all, the lesions of the lungs of these rabbits histologically were tubercle-like, but they differed from those lesions induced by virulent bacilli of bovine tuberculosis in remaining more or less discrete and in a marked tendency toward self-limitation, since evidence of progression was not observed.

COMMENT

These observations are of interest for two reasons: First, it appears that under certain conditions, which are more or less obscure, the *Bacillus Calmette-Guérin* has the ability to cause the formation in the lungs of rabbits of definite lesions which morphologically are not essentially unlike those of genuine tuberculosis. Second, whereas tubercle-like lesions of the lungs were distributed generally throughout the organ, the disease remained localized in the lungs and did not disseminate to such organs as the spleen, liver, and kidneys in a manner similar to that which occurs when virulent bacilli of bovine tuberculosis are injected. This would indicate that the acid-fast bacteria found in the tissue of the involved lungs either were dead or were in a state of greatly reduced vitality. That this probably was true was revealed by failure to secure cultures from the lesions containing the organisms, and by failure of the emulsions of the same tissue to induce lesions in rabbits and in guinea pigs.

Park and Mishulow reported the development of tubercles in the lungs of rabbits following intravenous injections of suspensions of *Bacillus Calmette-Guérin*, but in this case also the disease was not progressive.

The observations made in my study, however, were somewhat unusual, since I have been unable so far to duplicate the results.[3] My stock culture of *Bacillus Calmette-Guérin* has remained practically unchanged, although it has been more than four years since it was taken from Calmette's laboratory, and for the past thirty-four transfers it has been grown on a glycerine-egg-yolk medium.

In an earlier report (3) dealing with the behavior of this strain during the first fifteen generations in glycerine-egg-yolk medium, morphological evidence of limited pathogenicity was observed in guinea pigs inoculated intracerebrally. The disease produced, however, was not reinoculable, which seems to justify the conclusion that subculturing of the

[3] Additional experiments are being conducted.

organism on glycerinated egg medium has not enhanced its virulence appreciably.

That the culture medium in which the *Bacillus Calmette-Guérin* is grown may occasionally influence the state of pathogenicity of this organism was suggested by the work of Sasano and Medlar and of Dreyer and Vollum who grew the organism in liquid media. However the work of Boquet and, more recently, that of Park and his collaborators in failing to confirm the observations of Sasano and Medlar and of Dreyer and Vollum makes this phase of the problem difficult to understand.

My own observations seem to suggest that environment at times may have some influence on the subsequent ability of the bacillus to produce lesions; but the further fact that some obscure factors seem to prevent the regular repetition of a given result makes for the impression that the organism perhaps possesses a certain unpredictable instability, which one would prefer not to associate with a state of innocuousness. Although pathogenicity in the sense of Koch's postulates was not observed in these experiments, the fact remains that in all of the rabbits receiving the inoculum morbid changes developed, and in five of the animals the lesions were of a striking and extensive character; whether the infection was reinoculable or not, the resultant disease in the respective rabbits was too profound to be considered of no significance.

SUMMARY AND CONCLUSIONS

Using a strain of *Bacillus Calmette-Guérin* obtained from Calmette, in 1930, and grown for 20 generations subsequently on an egg-glycerine medium, glycerine-peptone-broth cultures were prepared and used to inoculate 6 rabbits intravenously and 4 guinea pigs subcutaneously. One of the rabbits died ten days after inoculation and the other five were killed 174 days after inoculation. Numerous and striking focal lesions, morphologically like tubercles, were found in the lungs of each of the 5 rabbits. Attempts to culture acid-fast bacteria from the lesions of the lungs were futile, although bacteria of this character were readily demonstrable in appropriately stained sections of the lesions. Emulsions prepared from lesions from each of the 5 rabbits failed to produce demonstrable lesions in other rabbits or guinea pigs, and attempts to repeat the results in later experiments failed.

These results indicate that the *Bacillus Calmette-Guérin* in the lungs of rabbits may at times produce numerous and extensive tubercle-like lesions.

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TUBERCULOSIS AS A CAUSATIVE FACTOR IN ADDISON'S DISEASE

With a Report of Cases

W. A. COLTON[1]

The adrenals are paired glands lying above the kidney and in close relation with it. Each gland consists of two parts, medulla and cortex, which, although anatomically united, are morphologically and embryologically distinct structures. They were discovered in 1563 by Eustachius, but it was not until Addison made his notable contribution in 1855 that their importance was known.

Embryologically the adrenal gland develops early. The cortex comes from the mesodermic cells of the genital ridge. Later the cortex is invaded by the ectodermal *Anlage* of the sympathetic ganglia, which differentiates into the chromaffin cells and sympathetic ganglion cells, which constitute the medulla. The medulla secretes the epinephrin. The function of the cortex is not definitely known, but it is indispensable to life. Removal of both adrenals from animals is followed by death within a few days, with the following symptoms: loss of appetite, apathy, muscular weakness, stiffness of the hind legs, subnormal temperature, fall in blood-pressure, labored respiratory movements, weak and irregular heart; muscular twitchings or convulsions may appear, and also profound prostration.

Addison's disease in man has an average duration of one to three years (Reisman (1)) or, according to Guttman's studies (2), thirty-four months when due to atrophy of the suprarenals, and 13.3 months when due to tuberculosis of the suprarenals. Incidentally, it may be stated that treatment by *escatine* or cortical extract is more efficacious in cases of atrophy than in those with tuberculosis of the glands.

According to Guttman, two theories may be advanced to account for the longer life of those cases having marked pigmentation of the skin; namely,

(1) that pigmentation is a manifestation of increased secretory activity of the suprarenal gland and (2) that the skin acts as a detoxifying agent and in this

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way compensates for the loss of suprarenal tissue. But the final solution rests on a deeper knowledge of the physiology of pigmentation and its relation to the function of the glands. But pigmentation may be a compensatory mechanism for the destruction of the adrenal glands.

Practically all investigators agree that males are more frequently affected than females. The age at which Addison's develops follows closely the death-ages of tuberculosis in general. The disease is progressive and seldom heals, and those with tuberculosis die more quickly than those with primarily contracted adrenals (atrophy). Regardless of which of these two major diseases cause the Addison's disease the symptoms do not greatly differ. Available experimental and clinical evidence points to the fact that the adynemia, the gastrointestinal symptoms, and the low blood-pressure are due to an accumulation of toxic substances subsequent to suprarenal destruction and that death is due principally to cortical failure.

It is a well-known fact that the Addison syndrome is not always present even in bilateral tuberculosis of the suprarenal glands. Guttman (2) surveyed the literature in 1930, and found that 69.72 per cent of cases of Addison's disease were caused by bilateral tuberculosis; 19.48 per cent by primary contracted adrenals (atrophy); 1.73 per cent by amyloid disease; 1.24 per cent by neoplasms; and that fatty degeneration, pressure atrophy, venous thrombosis, arterial emboli and syphilis caused the remainder.

According to Bell (3), and as a matter of common knowledge among all phthisiologists, adrenal tuberculosis is usually secondary to lesions elsewhere in the body, and is usually haemotogenous in origin.

The lungs seem to "have the call" as to the original focus in about 50 per cent of the cases, and hidden or active foci in other parts of the body in the remainder. An exacerbation of a previously quiescent lesion anywhere in the body may be brought on by intercurrent illness of any kind, exposure, overwork, overplay or any of the multitudinous causes of reactivating tuberculous lesions, from which the blood may bear the tubercle bacilli to any part of the body, including the adrenals. There appears to be a tendency to involvement of both glands as in other paired organs in the body, one first becoming affected, and later a metastasis to the other, probably aided by lowered resistance or allergic reaction. In bilateral adrenal tuberculosis the destruction of the organ is always more complete than in unilateral disease. In both, the medulla is more apt to be destroyed than the cortex of the gland, and, while caseation is the

rule, fibrosis of the capsule may be extensive. Tubercle bacilli are found in almost one-half of the specimens stained for their demonstration (Guttman). The tuberculous glands are enlarged and contain caseous nodules surrounded by gray connective-tissue bundles, and, in addition, areas which microscopically show marked tuberculous activity.

Nolan (4) in a statistical study of 1,250 autopsies found tuberculosis of the adrenal glands in twenty-two, or 3.2 per cent of these cases. In 602 deaths from tuberculosis, tuberculosis of the adrenals was the actual cause of death in three, or 0.49 per cent. In the same series, amyloid disease of the adrenals was found in four cases, or 0.64 per cent, but was not the primary cause of death in any case.

Tuberculosis of the suprarenal glands is seldom, if ever, a primary infection. In 243 autopsy cases in which the glands were involved in a tuberculous process Guttman found the following division of lesions elsewhere in the body: lungs, 124 (36 of these cases were healed scars); pleura, 45; disseminated miliary tuberculosis, 16; tuberculosis of the genitourinary tract, 38; lymph nodes, 54; other organs, 51. In thirty-one of these there was a history of tuberculosis from which complete recovery was made. Twenty-six were active at the time of the onset of the Addison's disease, twenty-seven had no history of previous infection, and one hundred and sixteen had a clinical history of active tuberculosis during the course of the disease.

Of the 8 cases of Addison's disease that died and were autopsied at this institution, all but two had tuberculosis of the adrenal glands. (One of these had tuberculosis and amyloid disease combined.) The two exceptions had amyloid degeneration of both adrenals. Twelve of our autopsied cases have shown tuberculosis of the adrenals (six without clinical symptoms of Addison's disease). Of the 8 cases all had tuberculosis elsewhere in the body, principally pulmonary, although three had arrested or healed pulmonary disease only, and one a moderately advanced slightly active pulmonary lesion. Two had genitourinary tuberculosis as a major condition. The tuberculous complications in these cases were as follows: gastrointestinal tract, 5; bone-and-joint tuberculosis, 2; tuberculous empyema, 2; amyloid disease of liver, spleen, and kidneys, 3; hyperthyroidism, 1.

Clinically all eight had a typical Addison's syndrome, including extreme weakness, gastrointestinal pains (usually cramps), nausea, vomiting, headaches, and loss of weight. Six had low blood-pressure (90/70 to 124/80).

Unfortunately the blood-pressure studies were not complete. Two cases were not recorded. Five had bronzing of the skin and mucous membranes to a varying degree. Three had visionary disturbances. Four had sudden collapse at death. One showed absent reflexes of the lower limbs, and one numbness of the arms and hands.

Case Reports

S. S.: White; male. This was one of the most interesting cases encountered at this hospital, hospitalized first in the Veterans' Administration Hospital at Minneapolis, Minnesota at age of 31. While the history and findings in this case are meagre, it is known that the patient complained of general weakness and underweight during two short periods of hospitalization in 1923, at Minneapolis, and at Fort Bayard, New Mexico. A diagnosis of moderately advanced arrested tuberculosis was arrived at on the final period of hospitalization. Blood pressure 124/80, pulse and temperature normal, and sputum negative throughout both periods of hospitalization. After discharge from Fort Bayard, New Mexico, A. W. O. L., the patient was apparently lost sight of, in so far as the Medical Service was concerned, until his widow appeared in June, 1933, and requested that the patient be disinterred and a postmortem performed. The reason for this request was that the man was cared for during his last illness by a Christian-Science practitioner whose diagnosis of far advanced pulmonary tuberculosis could not be accepted by the Pension Department; and the wife, therefore, would have been deprived of her widow's pension had not the autopsy been performed. The wife stated that the terminal illness lasted several months, and she and neighbors gave affidavits that the patient had an extensive cough with haemoptysis. In the light of the postmortem findings this is doubtful. However, there was one point which fits into the picture of Addison's Disease; namely, that death came very rapidly at the end. The patient made some remark to those at his bedside, then turned over, and expired.

Six months after death the autopsy showed a well-preserved cadaver. There was pronounced pigmentation of the forehead and lower portion of face. The subcutaneous fat was 1 cm. in thickness and the musculature appeared wasted. The left lung was free. The right lung was bound to the chest by dense fibrous adhesions completely obliterating the pleural cavity. The lungs were essentially normal, except for a calcified tubercle in the middle portion of the left upper lobe.

The other points of interest were as follows: Two rounded, firm, button-like nodules on the anterior surface of the liver which extended into the liver substance, measuring 1 cm. and 1.5 cm. in diameter. Within the substance of the liver several more such nodules were found. Both adrenal glands were

extensively infiltrated and almost entirely destroyed by caseous tubercles measuring from a few millimetres to 1 cm. in diameter. There was a tuberculous ulcer near the ileocaecal valve, and a tuberculous sinus extending from the left epididymis through the scrotum. The left epididymis was soft and caseous and the right epididymis contained caseous nodules. The prostate was moderately involved with tuberculosis. The cause of death was extensive bilateral tuberculosis of the adrenal glands, and the contributory cause tuberculosis of the epididymis. The calcified area in the lung was considered the original lesion, with a haematogenous spread to the epididymis with secondary infection of the prostate gland.

Histology: Section of left adrenal revealed a marked fibrous thickening of the capsule and extensive destruction of the gland; numerous infiltrated tubercles and large areas of necrosis and fibrous proliferation. The central portion of the gland contained a large area of calcification. A large area of acidophilic pinkish material surrounded this deposit, and this in turn was surrounded by a dense wall of epithelioid cells, surrounded by a zone of lymphocytes. The fibrous wall also contained occasional small lymphocytic foci and small solitary tubercles showing areas of necrosis at the centre, surrounded by epithelioid and giant cells, the whole structure being demarcated from the surrounding tissue by a zone of lymphocytes. The sections revealed occasional tiny areas between the extensive infiltrations of epithelioid cells and tubercle-formation which could be identified as adrenal cortex and medulla. The cells showed degenerative changes, and extensive fragmentation had divided them into tiny groups.

There was a dense fibrous capsule of the right adrenal, made up of colloidal fibrosis and epithelioid cells, which surrounded a homogeneous acidophilic mass which represented necrotic and degenerative tissue. There was no trace in any of the sections of normal adrenal tissue, the whole gland being entirely destroyed by the chronic tuberculous process.

Summarizing this case, the man undoubtedly had an early pulmonary tuberculous infection with tuberculous pleuritis, the process becoming arrested for a number of years, and a number of years later an embolus undoubtedly lodged in the epididymis extending to the prostate, with a spread to the adrenals, causing a true Addison's disease, resulting fatally. (See figure 1.)

G. H.: White; male; occupation, painter and decorator. This patient came into the hospital with a diagnosis of Addison's disease from the Swedish Hospital in Minneapolis, and is the only case admitted to the hospital with a diagnosis of Addison's disease. Admitted July 30, 1930; died August 6, 1930.

The family and personal history were negative except for the present ill-

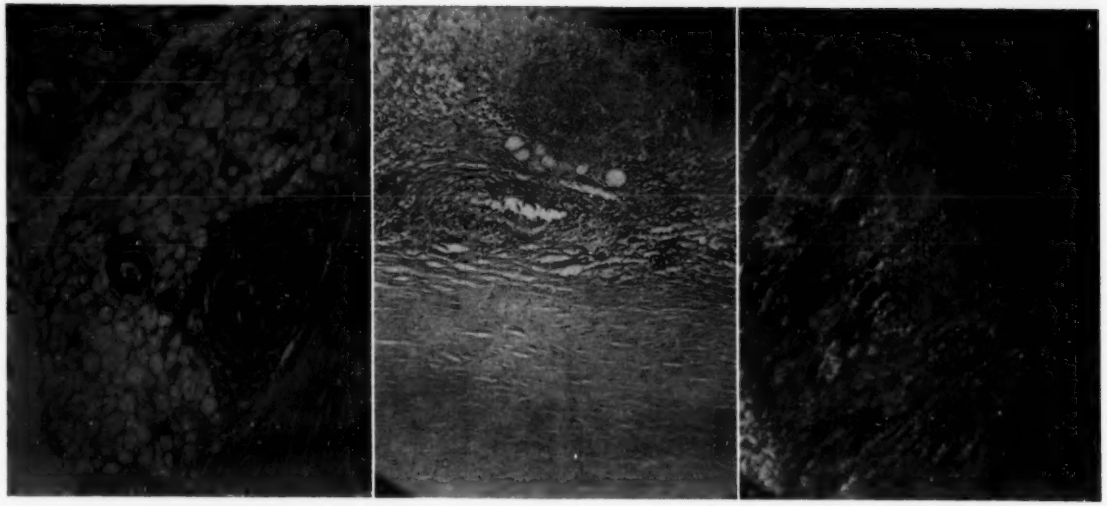

FIG. 1 FIG. 2 FIG. 3

FIG. 1. Patient *S. S.* Showing destruction of gland with large mass of caseation

FIG. 2. Patient *C. H.* Section through gland, showing caseation and fibrosis

FIG. 3. Patient *W. G.* Showing amyloid degeneration of the adrenals

ness. It shows that the patient quit work on May 27, 1930. On January 1, 1930, he began to have attacks of backache, poor appetite and loss of weight. His wife stated that he had always had a dark olive color. The patient said he had noticed a discoloration of his face for several years. He complained of constipation, weakness, nausea, and a dull burning pain at the umbilicus at times, burning on urination, blurred vision, and cold hands and feet. He had a cough for a week previous to admission to the hospital, mostly in the mornings.

Physical examination showed an emaciated man, with a pale, muddy complexion. Examination of the lungs disclosed diminished and markedly subdued to absent breath-sounds over the upper portion of the right lung; also a few sticky râles. The electrocardiographic study showed delayed A-V conduction and diphasic T in D-ii negative T in D-iii. Reflexes of the lower limbs were absent.

Urinalysis: Specific gravity 1010; acid reaction; trace of albumin; no sugar; a few pus cells; a few hyaline casts.

Blood Count: Total erythrocytes, 3,110,000; total leucocytes, 9,100. Differential leucocyte count: polymorphonuclears, 41; small mononuclears, 25; large mononuclears, 4; transitionals, 2; eosinophiles, 27; basophiles, 1. Haemoglobin, 60 per cent. Blood Wassermann, negative.

Treatment consisted of strychnine, adrenalin, a combination of adrenalin gland, gr. 2, with thyroid gland, gr. 1/2, and finally with suprarenal cortex. The patient failed rapidly and became very weak; pain in abdomen increased, nausea, vomiting and hiccough developed; and, as a terminal event, the patient had a chill followed by dyspnoea and visionary disturbance. The final event was sudden death.

At autopsy he was found to be emaciated, with estimated weight 100 pounds. There were a reddish hypostasis of the posterior and dependent portions of the body, and diffuse brownish pigmentation of the skin, which was accentuated in the anterior folds of the axillae, on the back of the elbow joints, and about the knees and anterior surfaces of the legs, abdomen and face. There were many small pigmented spots over the head and a small pigmented fleck on the buccal mucous membrane on the left side near the left angle of the mouth and a number of flecks on the upper lip.

Subcutaneous fat was abundant for the degree of emaciation. The loss of weight seemed to be in the musculature which was very thin. There was no free fluid in the pleural cavity. There were numerous adhesions between the pleural surfaces on each side; no active pulmonary tuberculosis; and the musculature of the heart was flabby and of a pale brownish-red color. The coronary arteries were of normal thickness and calibre throughout. No evidence of endocarditis. The only tuberculosis in the lung was a few calcified nodules in the apex of each upper lobe. Both suprarenals were moderately reduced in

size, surfaces were nodular and the organ was firm. The right was firmly adherent to the under surface of the liver. On section no normal cortex or medulla was visible. The parenchyma was occupied by firm encapsulated yellowish nodules of various sizes; also an abundance of scar tissue. *Diagnosis:* Bilateral tuberculosis of the suprarenals.

H. H.: White; male; age 43; occupation, meat-cutter. Readmitted as a terminal case of pulmonary tuberculosis with positive sputum three months after discharge against medical advice from this institution. Also had tuberculosis of the 9th, 10th and 11th dorsal vertebrae. Face and neck had been bronzed for about one year. There was a secondary anaemia with haemoglobin at 55 per cent. Man was unable to walk; had a marked terminal oedema of the entire body. Blood pressure 110/90. He had gained twenty-five pounds in weight since discharge, which was probably due to the oedema. In the year preceding death, which occurred about fifteen days after admission, the patient had developed many complications, including psoas abscess and paraplegia, amyloid disease of the liver and kidneys; also tuberculous cystitis. Patient complained of extreme weakness and inability to move limbs. The autopsy showed, in addition to the above antemortem diagnoses, bilateral tuberculosis of the suprarenal glands. The left was involved to a greater extent than the right. There was a caseous tuberculous abscess beneath the capsule of the liver.

C. H.: White; male; age 33; occupation, electrician. Admitted to this hospital July 1, 1929, as a far-advanced, class "C," case of tuberculosis. The case was rapidly fatal. Death occurred on July 19, 1929. History of tuberculosis extended back to 1924. Patient had seen many physicians and treated himself, but had not been previously hospitalized. Patient complained of being generally run down, had lost about 15 lbs. in last year, had slight morning cough with expectoration, had no appetite, had nausea after eating, was constipated, and suffered with night-sweats. Temperature on admission was 97.2°; pulse 78; general appearance was emaciated, pale and undernourished. Blood pressure, 90/70. The hypotension was considered secondary to the chest condition. Shortly after admission he complained of inability to retain food, which was considered as secondary to the toxaemia of this pulmonary condition.

Our gastroenterologist, in reviewing this man's temperature- and pulse-chart, both of which were below normal, was unable to account for these phenomena, and states "I know of no condition which would produce this picture. The pulse and temperature might go with a perforation or haemorrhage if the pulse had been higher. The physical findings do not show anything which might point to a haemorrhage or perforation."

The right testicle was found to be completely atrophied. Laboratory findings were as follows: Sputum negative for tubercle bacilli. Urinalysis showed faint trace of albumin and many bacteria. Blood findings showed: RBC, 5,120,000; WBC, 88,200; small mononuclears 56; large mononuclears 32; transitionals 9; eosinophiles 3; haemoglobin 95 per cent; coagulation time 7 minutes; Wassermann negative.

On the night before death the patient became very restless, got out of bed, suffered hallucinations, and, according to the nurse's report, "became very weak and limp-like with cold hands and feet." He revived to some extent following the administration of a cardiac stimulant, felt better, talked, and seemed quite natural. He again became weak and limp, and died very suddenly.

Autopsy showed a moderate purplish hypostasis in dependent portions of the body. The entire body was of a light brown color, particularly over the chest, abdomen, genitalia, back of the arms, and neck. The mucocutaneous border of lower and upper lip contained small irregular-shaped brownish pigment. There was a pigmented spot on the lower portion of the gingival mucous membrane beneath the first left incisor. The pulmonary tuberculosis was of only moderate extent, being confined to the upper lobes on both sides. There was no evidence of tuberculosis in the gastrointestinal tract nor in the genitourinary organs. Both adrenals were slightly increased in size and very hard. The capsules were thickened and there were adhesions to surrounding tissue. To quote from the pathologist's report: "The right adrenal measures 55 x 30 x 20 mm. Its surface is nodular. It sections with markedly increased resistance. Cut surface shows no normal cortex or medulla. The organ is replaced by a dense fibrous tissue containing small nodular masses of yellow caseous material. The left adrenal measures 50 x 30 x 20 mm. and shows changes similar to that of the right adrenal."

Microscopic examination of adrenals: "There are large areas of caseation. Some of these are well circumscribed by a dense wall of connective tissue and show little or no activity. Others show marked activity. Fibrosis is marked and extends for large areas about the caseous areas. In places small rests of cortical cells are present. No medullary tissue can be made out. The capsule is thickened and in places shows a penetration of the tuberculous process into the peri-capsular tissues. Examination of the sympathetic ganglia shows no evidence of inflammatory or degenerative changes."

This was considered a definite case of Addison's disease clinically, with bilateral tuberculosis of the adrenals as the cause. The gastrointestinal condition was evidently due to Addison's syndrome. (See figure 2.)

J. L. A.: White; male; age 38; occupation, none. Readmitted to the hospital April 24, 1933, as a service-connected case of tuberculosis of the right kidney. Clinical study proved involvement of both kidneys. Tubercle bacilli were found in the urine and on guinea-pig inoculation. Patient complained of weakness, pain in back, sore all over, frequent urination, rapid heart, shortness of breath, loss of weight (25 lbs. in last year). Blood pressure was 90/70. There was a history of a tuberculous epididymitis previously removed. The prostate was enlarged and nodular. The left seminal vesicle was tender and enlarged. On admission, appetite was good and bowels normal. Later on, the patient developed very great abdominal pain, belching, cramps, and pain in the lower abdomen. There was no jaundice. The abnormal findings shown on laboratory examinations were as follows: *Urinalysis:* Albumin 1 plus, — numerous leucocytes. *P.S.P.:* First hour 20 per cent; second hour 15 per cent; total 35 per cent. Blood chemistry showed urea nitrogen 21. X-ray and clinical findings of the chest were negative. The patient died June 26, 1933, and during the last period was drowsy, nauseated and vomiting continuously, later became irrational, and he died apparently of cardiac failure.

Autopsy showed the left pleural cavity obliterated by adhesions and a healed tuberculous scar of the right upper lobe. There was no active pulmonary tuberculosis found.

There was extensive tuberculosis of the bladder and kidneys.

Histopathology of the adrenal glands: There were extensive nodular areas with necrotic centres which were surrounded by epithelioid and giant cells. There were also a few monocytes and small lymphocytes adjacent to the cluster of epithelioid cells. The giant cells had nuclei which filled the peripheral zone. The adrenal cortex and medulla were almost entirely destroyed, only occasional small groups of glandular epithelium remaining. The kidney showed extensive areas of discrete and conglomerate tubercles. The tubercles had necrotic centres surrounded by epithelioid and giant cells. The renal tissue was rather extensively infiltrated by exudative cells, chiefly monocytes. A few of the glomeruli were hyaline and surrounded by small mononuclear cells.

Diagnosis: Tuberculosis of the adrenal glands, bilateral, extensive, and extensive tuberculosis of the kidneys.

J. R. A.: White; male; age 32; occupation, farmer. Admitted June 20, 1928. Died November 11, 1932. Blood-pressure on admission 120/80. Patient had a left unilateral pulmonary tuberculosis at the time of admission, positive sputum, and a stormy time throughout his entire hospitalization, with many complications developing, especially those referable to gastrointestinal tract and kidneys. However, on several occasions the urine was negative for tubercle bacilli.

Collapse therapy was instituted. Pyopneumothorax developed, and later the air was replaced by oleothorax (0.5 per cent gomenol). During treatment

he also developed spontaneous collapse, from which he recovered following deflation.

Amyloid disease of the liver, spleen, and kidneys was diagnosed three months before death, despite a normal blood chemistry. Bronzing of the face, abdominal cramps, weakness, headaches and dizziness were all present before death.

At autopsy all clinical diagnoses were confirmed and, in addition, a tuberculous appendix and tuberculous pleuritis were found, and the adrenal glands were markedly enlarged, very firm, and infiltrated throughout with amyloid, and, in addition, to contain many tubercles with caseous centres surrounded by epithelioid cells.

In this case the Addison's syndrome was apparently caused by a combination of tuberculosis and amyloid disease of the adrenals.

In the following two cases the Addison's syndrome was apparently caused by amyloid disease of the suprarenals:

W. G.: White; male; age, last admission, 35; occupation, electrician. Readmitted to this hospital for pulmonary tuberculosis September 2, 1931, after having left previously against medical advice. The patient had a long history of treatment for pulmonary tuberculosis beginning in 1923, and the disease had been progressive and the sputum positive since first diagnosed. No record of blood-pressure taken while in the hospital. Had been hospitalized at intervals since 1928. Attempts at artificial pneumothorax had been unsuccessful. During his period of hospitalization he was also operated upon for hyperthyroidism, with an increase in the symptomatology of his tuberculosis following the operation. During a previous admission he was very much interested in hospital activities, having organized a hospital broad-casting company and entertained the patients over a period of two years. He did not sense the seriousness of his condition, which contributed in a measure to the unsuccessful outcome. During the course of his pulmonary disease he developed tuberculosis of the 4th and 5th lumbar vertebrae, psoas abscess which was drained upon numerous occasions, tuberculous enteritis, and was troubled during the spring and summer seasons with severe high fever. About one year previous to death there was a marked bronzing on the face, neck, arms and hands. A diagnosis of tuberculosis of the adrenal glands was made four months before death, and the patient suffered from weakness, pain and cramps in the abdomen, and later diarrhoea, nausea, and vomiting. The abdominal pain later became so severe that it suggested appendicitis or a perforating ulcer. He was very nervous and agitated, and suffered with severe headaches. During the last week he developed numbness of the fingers, back and legs. While death was not actually sudden, he was unconscious for only two hours before the terminal event.

Autopsy confirmed all the antemortem diagnoses except tuberculosis of the adrenals; and, in addition, amyloid disease of the adrenals, liver, spleen and kidneys, and tuberculosis of the spleen were found. Sections of the adrenal gland surprisingly showed only extensive infiltrations of amyloid throughout the cortical portion, with no tuberculous involvement, being one of the cases in which tuberculosis was not the cause of the Addison's syndrome. (See figure 3.)

G. H.: White; male; age 37 on admission; occupation, bookkeeper. Admitted July 31, 1930, as a far-advanced, class "C" case of pulmonary tuberculosis. Very sick on admission, being delirious for a number of weeks. Shortly after admission he developed a tuberculous fluid in the left thorax, which later became a tuberculous empyema. The course of the disease was also complicated by tuberculous enteritis and amyloid disease of the liver, spleen and kidneys. The virulence of his condition was demonstrated by an interesting incident. During the course of a paracentesis by his ward-surgeon tuberculous fluid from his chest shot out suddenly following coughing and flew into the eye and nostril of the physician. Within a few days the physician became violently ill, developed a tuberculous pleurisy with effusion, for which it was necessary for him to take treatment for more than one year.

The patient later improved temporarily to a degree, but then had an extremely stormy time. A few months before death he developed a bronzing of the forehead, face and neck, together with extreme weakness and a marked drop in blood-pressure. At autopsy a lesion resembling tuberculosis was found in both suprarenal glands. These were whitish-yellow tubercles, from 2 to 3 mm. in diameter, and one large tubercle, 5 mm. in diameter, in the central portion of the right adrenal gland. On stripping the capsule of the adrenal there were many swollen tubercular areas. On microscopic section this tubercular condition proved to be amyloid disease. Amyloid disease of the liver, spleen, and kidneys and fatty degeneration of the liver were also found.

The six remaining cases studied in this review all died of pulmonary tuberculosis without signs of Addison's disease during life, and tuberculosis of the suprarenals was found at autopsy as a part of the tuberculosis picture. All were white males, ages thirty-seven to forty-seven. The blood-pressure range varied between 78/68 and 130/80. All had tuberculous complications as follows:

Tuberculosis of larynx	3
Tuberculosis, general miliary	3
Tuberculous enteritis	3

Tuberculous colitis.....3
Tuberculous meningitis.....1
Pleurisy with effusion.....1
Ascites.....1
Tuberculosis of the kidneys.....2

with nontuberculous complications as follows:

Syphilis.....1
Severe haemorrhage.....1
Pericarditis.....1
Delirium tremens.....1

All had tuberculosis of the suprarenal glands, classified as follows:

1. Small scattered tubercles, both glands
2. Beginning tuberculosis of both glands
3. One gland involved, side not stated
4. Both glands to a minimal degree, more on the right
5. Both glands contain scattered tubercles
6. Few small tubercles in cortex both glands

The average period of hospitalization in the cases suffering with Addison's syndrome was as follows:

Those suffering with tuberculosis.....40 days
Those suffering with amyloid disease only.....704 days
One suffering with a mixture of tuberculosis and amyloid disease of the adrenals.....1,604 days

Summarizing the 14 cases reported in this series, five had Addison's disease due to tuberculosis of the adrenal glands; two due to amyloid disease of the adrenal glands; and one due to a combination of both conditions; six cases of tuberculosis of the adrenal glands without symptoms of Addison's disease are also reported.

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EXPERIMENTS ON THE FILTERABILITY OF TUBERCULO-VIRUS[1]

E. PIASECKA-ZEYLAND AND J. ZEYLAND

The problem of the filterability of the tuberculous virus, started by Fontes (1910), taken up by Vaudremer (1923) and by Calmette and Valtis (1924), became a chief matter of controversy in the last decennium, demanding attention and examination from every worker in tuberculosis.

In this paper we report the results of our researches concerning this problem, and present a control of some methods employed by several authors in the last years.

1: The primary method (the detailed technique as elaborated by Valtis) consists in the filtration of tuberculous material or of tubercle bacilli cultures through Chamberland candles and in injection of the filtrate into guinea pigs, which show enlargement of the lymph nodes, especially of the mediastinals, with presence of acid-fast bacilli, which regain sometimes their former virulence in the course of the successive animal inoculations.

This method was employed by us in only few cases: the filtrates of two cultures (Ratti and Vallée from Pasteur Institute) and 5 specimens of tuberculous or presumptively tuberculous (in the meaning of the adherents of the filterability theory) material, such as caseous lymph nodes, foetus and child of tuberculous mothers, blood of tuberculous mother, hydrocoele, were injected into 17 guinea pigs. It was impossible to detect in any case acid-fast bacilli in lymph nodes or other organs of these animals. We soon gave up this method (by which rarely even the primary authors have got positive results) in favor of the following methods recommended as more certain.

2: The method of van Deinse consists in a more rapid detection of acid-fast bacilli by the intraperitoneal injection of calcium phosphate before the injection of the tuberculous filtrate. The calcium phosphate causes abscesses of the omentum, in which the discovery of acid-fast

[1] From the Microbiological Institute (Professor L. Padlewski) and the Clinic for Children (Professor K. Jonscher) of the University of Poznań, Poland.

bacilli is said to be easier. Exactly following the direction of van Deinse we injected 10 different filtrates of tubercle bacilli into 18 guinea pigs. We saw, to be sure, small abscesses and necrotic foci in the omentum, but no acid-fast bacilli.

3: The method of Nègre is the application of the so called (by English bacteriologists) "tissue depressants." Nègre injects subcutaneously for a longer time, and twice a week (at least 6–7 times) an acetone extract of tubercle bacilli into guinea pigs supposed to have the ultravirus either as the result of tuberculous-filtrate injections or as derived from tuberculous mothers. This extract, according to the author, favors the development of tuberculous lesions and even renders possible an earlier cultivation of tubercle bacilli from these animals.

Thanks to the kindness of the author we received the acetone extract and used it in 44 guinea pigs inoculated either with tuberculous filtrates or (in the second passage) with the organs of the preceding guinea pigs inoculated with filtrates. With the exception of 2 cases, also here all results were negative. In two guinea pigs, in the lymph nodes near the place of injection, single acid-fast bacilli could be detected. The origin of the bacilli is explained by examination of the acetone extract, which, as known, is cleansed from bacilli by filtration through blotting-paper. Indeed, the extract sediment showed very scarce but characteristic acid-fast bacilli. This explains sufficiently our supposed positive results in the two cases.

4: The method of Sanarelli merely consists in the removal of inaccurate porcelain filters and the application of ultrafilters of collodion. Sacs of collodion were prepared, according to the direction of Sanarelli and Alessandrini, and filled with 10 mgm. of a culture of Bacillus Vallée. Dr. Dega put these sacs intraperitoneally into 12 guinea pigs. In part of the cases we inoculated the pathological tissues, obtained in the first passage, into new guinea pigs (second passage), and finally again into further guinea pigs (third passage). We used for the purpose 26 guinea pigs. The pathological changes in the first passage resembled those described by the Italian authors:—plastic peritonitis (with epithelioid cells and sometimes even giant cells), proliferation of reticuloendothelial tissue of the lymph nodes and omentum, with abscesses, necrotic foci and acid-fast bacilli. The bacilli could be cultivated very easily, contrary to the statement of Sanarelli and Alessandrini. The lesions observed by us we consider as a very acute form of tuberculosis (hence for the most part lack of specific histological signs of tuberculosis) caused

by massive penetration of tubercle bacilli. We saw quite similar lesions after inoculation of massive doses of tubercle bacilli (10 mgm.) directly into the peritoneal cavity. Further inoculation of the lesions obtained in the first passage into new guinea pigs provokes the gradual appearance of typical tuberculous lesions in consequence of the diminution of the infecting dose. Therefore these investigations too did not corroborate the observations of the primary authors.

5: To the method of Panek we devoted most time because Professor Panek (to whom we are greatly indebted), as our fellow-countryman, aided us by supplying us with his *tuberculotensin* which plays such a rôle in this method, and by technical advice. The method of Panek consists in transformation *in vivo*, in tuberculous guinea pigs, under the influence of *tuberculotensin* injections, of visible forms of tuberculous virus into invisible elements. The presence of these invisible elements is to be proved by the inoculation of organ filtrates of such treated guinea pigs into new guinea pigs, which succumb after successive passages to typical tuberculosis; or (and it is the essential fact in the investigations of Panek) by inoculation of such a filtrate in a special medium (modified Martin's broth) to obtain the granular forms. We tried this method during some years, inoculating, according to the direction of Panek, 104 guinea pigs and making 77 cultures, but obtained only negative results with the exception of 3 cases. Three cultures yielded cocci presenting an appearence like these of Panek, but without all the characteristic qualities demanded by this author. Therefore we did not try to obtain acid-fast bacilli from these cocci.

SUMMARY AND CONCLUSIONS

Summarizing our observations, based on the examination of 209 guinea pigs and 77 cultures, we have to state that our attempts to substantiate the quoted methods of demonstrating the filterability of the tuberculous virus have given us only negative results. Comparing them with the results of other authors, we are certain that they cannot decide the problem of filterability in tuberculosis. A critical review of the literature on this question shows equally among adherents and antagonists of the theory of filterability important works and prominent names. But one fact is striking, namely, that among the adherents every worker obtains positive results exclusively by his own technique; none of the described methods have given positive results in the hands of other authors not belonging to the same school; in other words, these experiments are

marked by lack of ability of reproduction and that is the main obstacle to the general acknowledgment of a fact in experimental science.

The problem of the filterability of tuberculous virus, so we think, demands still further investigation with the application of new methods, and at present this question is of no practical importance in the *Klinik* of tuberculosis.

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THE PROGENY OF THE TUBERCLE BACILLUS[1]

STEPHEN J. MAHER

At the International Conferences on Tuberculosis held in Brussels in 1910, and in Berlin in 1913, I presented papers on the general topic suggested in the title to the present paper; but the findings reported in these two papers were mostly accidental and bore little or no relation to one another. The findings reported in to-day's paper are the result of a definite technique which, if applied to any full-grown culture of tubercle bacilli, will cause the bacilli to give birth to cocci and diplococci non-acid-fast, that produce an acid harmless to themselves but full of harm to the bacilli from which they are derived. I rather jocularly suggested to some of my medical and official friends who knew the nature of my recent work, that a suitable title for this paper would be "How to Coax Tubercle Bacilli to Commit Suicide;" but they insisted that such a title would be too flippant. Therefore I appear before you with the more serious title of "The Progeny of the Tubercle Bacillus."

In the fall of 1908, I received from my friend, the late Dr. Leonard Pearson of the University of Pennsylvania, several tested strains of tubercle bacilli. Among them was a human strain designated *HPii* (Human Pennsylvania ii) that interested me very much because of the faintly yellow color of its colonies on glycerinized media. I made plantings from this culture on all sorts of media and kept some at room temperature and some at 37°C. After a few months, in many of the ageing cultures at 37°, I found, mixed with the granular tubercle bacilli, pale blue cocci and diplococci. With much difficulty I was able to separate the cocci from the bacilli and to grow them pure on ordinary non-glycerinized media; and I was delighted to note that subcultures on glycerinized media, preserved the same faintly yellow chromogenesis that the original pure cultures of the tubercle bacillus had displayed. During the following years I studied this coccal derivative of *YHPii* (Yellow Human Pennsylvania ii) in various ways. I found that it did not cause tuberculosis in laboratory animals, but for a long while I was

[1] The opening address at the Tuberculosis Conference held November 13, 1933, at Laurel Heights State Sanatorium, Shelton, Connecticut.

convinced that it had some badly understood influence on guinea pig and rabbit tuberculosis, and I was emboldened to administer killed cultures to tuberculous patients. However, its action was uncertain, and I gradually lost interest in it, although I have yet some cultures of it.

It must have occurred to every laboratory worker, who has studied flask-cultures of tubercle bacilli kept at 37°C. for a year or so, that, in the crumbling bacillary mass in the bottom of the flask, there were occasionally to be found a few non-acid-fast cocci and diplococci in fields of granular acid-fast and non-acid-fast bacilli, and that plants from this mass resulted in subcultures of pure growths of more or less acid-fast bacilli. I first reported this finding at Brussels in 1910, and again in Berlin in 1913. My interest in this phenomenon has been recently revived by a conversation I had at Hamburg in the summer of 1932 with Professor Møllgard of Copenhagen. In his study of the question of the incidence of tubercle bacilli in the blood of consumptives, he said to me that he had not found entire tubercle bacilli in the blood of tuberculous patients but that, during acute febrile stages of cases of pulmonary tuberculosis, he had frequently found in patients' blood fragments of tubercle bacilli that seemed to correspond to the granules or beads of old tubercle bacilli cultivated *in vitro*, and that from these granules he had been able to grow cocci and diplococci that resembled pneumococci.

On my return to New Haven, I found among other material in my incubator a glycerin-broth flask of H60, the well-known Saranac strain of human tubercle bacilli. It had been planted on February 17, 1932. At first it had shown very poor growth. The crumbs on the surface of the medium were not much larger in two weeks than at the time of planting. I therefore had planted in this flask on March 4, 1932, more H60 from a vigorous glycerine-agar culture. The pellicle soon covered the surface of the medium and before my vacation in August a series of pellicles had fallen to the bottom of the flask. During my absence of seven weeks attending tuberculosis conferences in Europe, the current of electricity had been shut off from my incubator and the culture had therefore been at room temperature during all that time. Now, on my return in October, I set myself to the task of studying this flask of tubercle bacilli. My first smears from it disclosed "patches of pink and flesh colored matrix or symplasm sprinkled with old granular, sometimes filamentous and beaded acid-fast tubercle bacilli." With gram staining, I found "granular positive bacilli in a mass of negative matrix or symplasm." The flask was now put at 37° again. Twelve days later I

made other smears. My note of this date records as follows: "Large non-acid-fast cocci, and tubercle bacilli that have lost their granules. Relation suggested. The tubercle bacilli are often attached at one end to a blackish blue coccus darker than nearby blue cocci which however seem to be derived from the darker coccoids. The suggestion that all the cocci or diplococci are derived from the black granules or polar beads of the tubercle bacilli seems to me irresistible. The absence of the granules from the shrunken gram positive tubercle bacilli, and the abundance of the cocci in every field, seems to me confirmatory of the above suggestion."

In the hope of encouraging the independent growth of the non-acid-fast cocci and diplococci and to discourage the growth of the tubercle bacilli, I added 50 cc. of sterile litmus milk to the 250 cc. of medium in the flask of glycerin-broth, and removed the flask from the incubator and put it aside in a cupboard at room temperature. Gradually the tubercle bacilli disappeared from the flask and were replaced by the beautiful non-acid-fast cocci and diplococci. Subcultures from the flask on all the ordinary liquid or solid, plain and glycerinized media gave prompt, pure and generous growths of these cocci and diplococci. However, they neither caused nor prevented tuberculosis in guinea pigs. In many previous papers, I have reported that I carry in stock in my laboratory strains of changed bovine and human tubercle bacilli, so changed that they grow best now at room temperature and grow almost entirely non-acid-fast and nonpathogenic but still preserve the characteristic of becoming granular and polar-beaded as they grow old.

A year ago, I had several old flasks of these transmuted types growing at room temperature. It occurred to me that it would be interesting to try to get some coccal derivatives from these old cultures that now consisted of bacilli, non-acid-fast and acid-fast, in the proportion sometimes of 20 to 1, and sometimes of 100 to 1. I selected for this experiment chromogenic, nonpathogenic descendants of Koch 1 strain from Saranac Lake (Red K1), and of (H37) of Saranac Lake (222), and a bovine (Blue Bovine), and a human, (RRH) from the laboratory of Dr. Nathan Raw of London, formerly of Liverpool, England. All four cultures were many months old and in none of them were there yet any cocci or diplococci. Red K1 and 222, because they had not entirely lost their power of growing at 37°, provided the more difficult problems. The Blue Bovine and the RRH, because they could not now vegetate normally at 37°, were easily made to surrender their contained granules as cocci. It was necessary merely to add 20 per cent of sterile litmus

milk to their flasks and then to put the flasks in the incubator, to force the granules to erupt from the bacilli and to begin to grow abundantly in the milk and to develop sufficient acid in the flasks to cause the disappearance of all the bacilli. As with the flask of H60, described in the beginning of this paper, subcultures from the flasks of Blue Bovine, 222, and RRH, to which milk had been added, gave pure growths of cocci and diplococci, grossly identical with the subcultures from H60, and microscopically and in staining reactions practically identical. There were some discrepancies in size and in adaptibility to grow on various media, but altogether subcultures of all four strains were similar. Because Red K1 grew at 37° as well as at room temperature, it required a little more patience, and a second addition of milk to force the granules from the old bacilli,—the peas from the pods, as it were,—but finally the cocci appeared and were subcultured. But, sometimes after making successful subcultures, if one put the Red K1 flask of glycerin-broth and milk in the incubator, the bacilli of the mother colony would take on a new interest in life and would vegetate normally as bacilli and outnumber the cocci, and after a week become the sole living occupants of the flask of glycerin-broth. Subcultures would give only pure growths of the more or less acid-fast rods, and would form pure red pellicles on the surface of the milk and glycerin-broth medium.

All the heretofore described findings were of course interesting even though they were not uniform; but they did not satisfy me because they did not permit me to formulate a definite rule which, if followed, would invariably reduce cultures of tubercle bacilli to cultures of cocci and diplococci. It so happened that in April, 1933, I had occasion to give a talk on the tubercle bacillus to the biology class of the Girls' College of Albertus Magnus. In preparation for this event, I called on Dr. Edward J. Lynch, Superintendent of the Laurel Heights State Tuberculosis Sanatorium for a few old cultures of tubercle bacilli that I knew he had in stock. He kindly sent me some sixteen cultures of various strains of tubercle bacilli growing on glycerin-agar and a modified Petroff medium. When the lecture event was over, he left eight of these old cultures in my laboratory. It occurred to me that these cultures could perhaps be made to answer some of the questions still unanswered in my mind as to the possibility of systematically transmuting tubercle bacilli into cocci and diplococci. I have now tested these eight cultures and nine others and with such uniform results that I feel that I should publish my findings.

The strains of tubercle bacilli received from Dr. Lynch, of Shelton,

and their laboratory numbers and their respective ages were as follows. The medium called *modified Petroff* was ordinary Petroff medium without gentian violet.

Shelton no. 1 = H60 planted on glycerin-agar, March 9, 1932
Shelton no. 2 = H60 planted on modified Petroff, August 13, 1932
Shelton no. 3. = Culture from cervical lymph node, and planted on modified Petroff, June 18, 1932
Shelton no. 4 = Culture from pleural pus planted on modified Petroff, January 25, 1932
Shelton no. 5 = H60 planted on glycerin-agar, March 30, 1932, plus room temperature, May 24, 1932
Shelton no. 6 = H60 planted on modified Petroff, January 18, 1933
Shelton no. 7 = H60 planted on modified Petroff, August, 1932
Shelton no. 8 = Strain of tubercle bacilli isolated from tuberculous cervical lymph node of a patient at Laurel Heights Sanatorium, then injected into a guinea pig and recovered from the spleen of guinea pig and planted on modified Petroff medium, June 18, 1932.

Microscopical examination of smears from all 8 tubes demonstrated that they were all pure strains of tubercle bacilli, except that in the older cultures the acid resistance of the bacilli had begun to diminish and in the strain labelled *Shelton 3* there were a few faintly blue bacilli, and in all 8 tubes many acid-fast bacilli were black-beaded and granular, and infrequently a red or blackish granule grew free from its bacillary pod.

One of the flasks of glycerin-broth, marked *Shelton 11*, I planted on April 27, 1933, from a glycerin-agar culture of H60, Shelton 1, in the ordinary way of floating a few crumbs of the mother culture on the surface of the glycerin-broth. On May 16 when there was a good pellicle on the surface of the medium in this flask, and when smears from this pellicle showed under the microscope a pure culture of acid-fast tubercle bacilli, some of which were already granular, I poured into the flask 50 cc. of litmus milk and put the flask at room temperature. The amount of milk was sufficient to give grossly a uniform pale blue color to the whole content of the flask. The history of this flask with its young culture of H60, as compared with the history of the seven other flasks that contained old cultures of tubercle bacilli, can best be told a little later. At this point, it will make my thesis more intelligible if I say a few words, as of self-revelation, a few words as to my state of mind, as

I face the problems of changing these 8 old Shelton cultures of tubercle bacilli into non-acid-fast cocci and diplococci. This metamorphosis I had been able to effect with the nine-months-old glycerin-broth culture of H60, and with old cultures of only partially acid-fast cultures of Blue Bovine and H37 and of Red Koch 1, and with Y Human Pii from the University of Pennsylvania. What now would be the best technique to follow in my endeavor to change the 8 Shelton cultures of pure tubercle bacilli? I decided to test, first, Shelton 1, 2, 3 and 4. Cultures 1 and 2, you remember, were of H60; no. 3 was from a tuberculous cervical lymph node, and no. 4, from tuberculous pleural pus. I poured 2 cc. of plain broth into all 4 tubes of culture, carefully scraped the bacterial growth from the solid medium, and poured the resulting emulsions into 4 flasks, each containing 250 cc. of glycerin-broth; added 50 cc. of sterile litmus milk; and put all 4 flasks in a dark cupboard at room temperature.

After four days, a whitening of the litmus blue was noticeable for a quarter of an inch of the surface of the medium, or in the lower sixth of the flasks marked *Shelton 1, 2, 3* & *4*; and, in nos. 1, 2, and 3, the microscope revealed at this time, besides granular tubercle bacilli, many free red and blue granules, and, in no. 4, many beautiful and perfect blue cocci and diplococci. On the sixth day, perfect blue cocci and diplococci were present in all four flasks, in company with clumps of black-beaded acid-fast tubercle bacilli. Subcultures from the flasks into glycerin-broth and litmus milk and glycerin-agar gave but cultures of non-acid-fast cocci and diplococci of the general size and appearance of pneumococci. Mixed with these pseudo-pneumococci were often a few disintegrating granular tubercle bacilli. Further subculturing from the first subcultures invariably gave pure growths of the non-acid-fast and poorly gram-positive cocci and diplococci.

The two remaining Shelton cultures of tubercle bacilli were now tested for confirmation of the results in nos. 1, 2, 3 and 4. To both of these cultures, nos. 5 and 6, a special interest was attached because of their youth. No. 6 had been planted, as I have already indicated, on January 18, 1933. I feared that it would not submit to my coaxing to erupt its contained granules in such a way as to permit me to grow them as cocci and diplococci, and in fact it proved a more difficult problem than any of the other Shelton cultures.

No. 5 also had a peculiar history. It had been planted on glycerin-agar on March 30, 1932, but it was kept at 37° not quite two months.

It had been at room temperature since May 24, 1932. Both were cultures of H60 and the microscopic findings in the original tubes according to my notes made on May 16, 1933, were as follows:

5 Shelton—black-beaded tubercle bacilli
6 Shelton—black-beaded tubercle bacilli but bacilli and beads are smaller than in no. 5 and many beads are free

On this same day, May 16, 1933, I poured a few cubic centimetres of plain broth into the original tube cultures of 5 and 6, scraped off the bacillary growth, and poured the resulting emulsions into two flasks, containing each 250 cc. of glycerin-broth. I kept both flasks at room temperature for 24 hours and then at 37° for 48 hours, and then at room temperature at which they have remained ever since. The hoped-for changes in the gross appearance of the contents of the flasks 5 and 6 were slow in coming, and the changes revealed by the microscope were not the desired ones. The acid-fast bacilli slowly lost their acid-resistance and became more and more granular. On May 21, 1933, tiny dots (promises of coming cocci) appeared in both flasks, but, as there was as yet no change in the gross appearance of the medium, I poured into each flask 30 cc. of sterile litmus milk. Now the litmus of the no.-5 flask began to whiten, and smears made on May 25, 1933, contained in every field hundreds of beautiful blue cocci and diplococci which were easily subcultured pure. However flask 6 was still resistant in gross appearance and the microscope showed only a few acid-fast coccoids and clumps of granular acid-fast rods, and all subcultures made as late as May 29 gave no growths of any kind. Somewhat discouraged over the behavior of flask 6, I decided to try on it the effect of plain broth. Plain broth is of course a difficult medium for tubercle bacilli and a good medium for most non-acid-fast organisms. On May 31, 1933, I poured into flask 6, 200 cc. of plain broth of tested sterility. The number of polar-beaded non-acid-fast tubercle bacilli slowly increased and a whitening and digesting of the litmus milk began. Smears made June 11, 1933, showed, besides the non- or poorly acid-fast bacilli, a few perfect blue cocci and diplococci in every field. Smears made twelve days later, on June 23, 1933, showed a pure culture of beautiful rather small blue cocci and diplococci and the entire disappearance of all bacilli, acid-fast and non-acid-fast. Subcultures on glycerin-agar, whether at 37° or at room temperature gave prompt and pure cultures of these cocci and diplococci.

Subcultures in milk did not change the milk but a certain proportion of the cocci and diplococci grew acid-fast.

Therefore, I have had a 100 per cent success in transmuting all 6 strains of tubercle bacilli, 4 of H60 and two of Shelton isolation, into cocci and diplococci, in many ways resembling pneumococci. There remains however for explanation flask 11. The tubercle bacilli used in flask 11 were from the same source as those used in flask 1, but for flask 11 they were secured not by scraping all the culture from the medium, and, as in flask 1, pouring the resulting tubercle bacilli emulsion into a flask of glycerin-broth. The ordinary technique of subculturing, by floating a few crumbs of the tubercle bacilli on the surface of the glycerin-broth, was followed with flask 11. No milk was added to this flask until 19 days after the planting. At the time of the addition of the milk, the flask was put at room temperature. When the milk was added there was already formed on the glycerin-broth a good actively growing pellicle of pure tubercle bacilli, which of course was broken up when the milk struck it. This flask therefore presented a different problem from flasks 1, 2, 3, 4, 5 or 6. Eventually the same result was secured as with the others, but not until some puzzling phenomena were encountered. The milk-broth mixture of flask 11 was slower in forcing the tubercle bacilli to disgorge their contained granules and, when these granules were disgorged, they grew free in the medium, not as cocci or diplococci, but as tiny non-acid-fast rods about one-fourth to one-tenth the length of an average tubercle bacillus. Room-temperature plants from flask 11 on glycerinized media gave good growths of these tiny rods for several generations; and, on Petroff's gentian-violet media and in litmus milk, many of these tiny rods, especially those in the centres of clumps or masses, became strongly acid-fast. They were shorter than tubercle bacilli and were entirely stained. However, subcultures at 37° on any ordinary solid or liquid medium became pure cultures of the usual cocci and diplococci, often suggesting pneumococci in size, shape and staining. After standing at room temperature for some weeks flask 11 became more markedly acid, formed characteristic curd and whey, and lost its faculty of producing tiny rods, and itself became a pure culture of non-acid-fast cocci and diplococci, smears revealing no rods, long or short, and nothing acid-fast. The subcultures, obtained from flask 11 in the first days after the birth of the tiny rods and kept at room temperature ever since, continue to show only tiny rods, both non-acid-fast and acid-fast.

No. 8 Shelton

The following notes from my laboratory records explain themselves:

July 30, 1933: To-day I began another chapter of the story of my efforts at transmuting old tubercle bacilli into cocci and diplococci that resemble pneumococci. My material to-day was another of the tubes sent to me from Shelton Sanatorium, containing a pure culture of tubercle bacilli, and which has been standing since the middle of April at room temperature on a rack on the sunless side of my laboratory. Up to April, 1933, it had been kept continuously at 37° from the date of planting at Shelton. This strain was isolated from the pus of a tuberculous cervical gland of a patient at Shelton. The pus had been injected into a guinea pig, and from the guinea pig had been recovered in pure culture. In the tube under consideration, it had been grown on modified Petroff medium. My laboratory name for this culture is "8 Shelton."

Smears from the tube revealed: "Brightly acid-fast thin, granular and beaded tubercle bacilli. Many red beads free carrying with them a red shred of the mother bacillus."

When this growth was scraped off the medium into 2 cc. of plain broth and the emulsion poured into a flask of glycerin-broth, the mixture in the flask after a few hours at 37° showed only small clumps of pure thin granular tubercle bacilli, nothing non-acid-fast. Fifty cubic centimetres of litmus milk was immediately added to the flask which contained 250 cc. of glycerin-broth. After 48 hours there was no change in the gross appearance of the flask. It was still blue from the litmus milk. My note of August 1, 1933 was as follows:

August 1, 1933: This morning at 10 o'clock, I made smears from 8 Shelton flask, which I had put at 37° yesterday for four hours and had then returned to room temperature. The microscope showed only the same picture as the smears of yesterday. (Fragmenting small red tubercle bacilli. A few fragments blue but no perfect cocci or diplococci. A few black beads free. There were a few blackish-red beads free but no perfect blue cocci or diplococci. I therefore put the flask back in the incubator at 37° in the hope of hurrying on the transmutation intending to leave it there for 48 hours. Tonight 11 hours later, there is no change in the gross appearance of the flask. Nevertheless I made some smears, and some subcultures on glycerin broth and glycerin agar. To my surprise and delight, I find in the smears many perfect blue cocci and diplococci. I anxiously await the coming of the morrow, hoping to find growth of non-acid-fast cocci and diplococci.

My notes of August 2, 1933, showed that although there was yet no gross change in the contents of the flask, the microscope showed that the beautiful non-acid-fast cocci and diplococci now outnumbered the fragmenting tubercle bacilli, and the subcultures attempted the preceding evening were not fully successful for 48 hours when my notes read as follows concerning last evening's plant in glycerin-broth: "Beautiful cocci and diplococci blue. A few disintegrating and fragmenting red t.b. showing relation of blue cocci and diplococci to the beads of the tubercle bacilli."

The note on the glycerin-agar culture was simply, "Pure pale blue cocci and diplococci."

The rest of this chapter is merely that now the flask began to whiten, and in three days the contents had become one-quarter curd and three-quarters whey, the tubercle bacilli had practically disappeared, and the flask contained an almost pure culture of acid-producing cocci and diplococci.

Subcultures made late in the evening of August 1 and on August 2 at 37° and at room temperature on glycerin-broth, glycerin-agar, and litmus milk gave in 24 hours and 48 hours only pure growths of non-acid-fast cocci and diplococci. No bacilli of any kind and nothing acid-fast remained. Not always do the tubercle bacilli disappear so rapidly. It is frequently necessary to make a second subculture before the tubes contain only the non-acid-fast cocci and diplococci.

The label on the tube, containing strain Shelton 7, had fallen off and got lost. I did not test it in its turn because I wanted to learn from Dr. Lynch its history. He reported that it was H60 and one year old. Following the formula already described, I quickly transmuted the acid-fast bacilli into non-acid-fast cocci and diplococci.

Dr. Lynch gave me early in August three more cultures,—nos. 9, 10 and 12 Shelton. They were easily broken down into non-acid-fast cocci and diplococci. No. 9 was of special interest to me because it was a heavy growth on Petroff's gentian-violet-egg medium. I wondered whether the inhibiting power of the gentian-violet might not interfere with the development of the coccal organisms. It did not.

Thus far in this study, I had been using only flasks of glycerin-broth in which there were good growths of pure tubercle bacilli, or flasks of glycerin-broth into which I poured the scraped-off growths of pure tubercle bacilli. Three questions naturally arose in my mind:

1: Cannot the same results be obtained by using, instead of flasks, ordinary tubes of glycerin-broth and adding the milk to these tubes after pouring the tubercle bacilli into the broth?
2: Is it necessary to pour the tubercle bacilli into the broth first? Why not pour the tubercle bacilli into tubes of milk and then add glycerin-broth?
3: Cannot the same transmutation be effected by pouring the tubercle bacilli into the broth alone or into the milk alone?

The answer to question 3 is "No." The tubercle bacilli in broth alone or in milk alone remain tubercle bacilli whether kept at 37° or at room temperature. Unless the cultures are many months old the non-acid-fast cocci and diplococci do not appear in the flasks or tubes.

The answer to question 1 is that the same results can be obtained with tubes as with flasks, but not with the same regularity. Thus far I have never failed with the flasks to get the non-acid-fast cocci and diplococci and to have the contents of the flasks become acid and turn into curds and whey. Even in the tubes a mutation of the tubercle bacilli takes place, but it is often very slow and the results are often tiny non-acid-fast bacilli and no cocci or diplococci. In 24 tubes that, five and six weeks after planting, I reviewed on September 30th, I found cocci and diplococci in all, but often in small numbers and sometimes mixed with tiny blue rods and in many a persistence of fragmenting tubercle bacilli or acid-fast coccoids. In several of the tubes that contained pure blue cocci there was little or no acidifying of the litmus milk. May not the explanation of this phenomenon be the difference between the great amount of surface that the medium in the flask exposes and the relatively smaller surface area in the test tubes? Even in the flasks it is usually on or near the surface that the non-acid-fast cocci and diplococci first appear among the nonbeading tubercle bacilli.

The answer to question 2 is that it seems to make little difference whether the tubercle bacilli are poured into the milk before the addition of the broth, or are poured into the glycerin-broth before the addition of the milk. In fact in my experiments with tubes, the pouring of the tubercle bacilli into the milk first has been somewhat more successful than the reverse process. The final results are about the same, but the development of acid is quicker when the tubercle bacilli are poured into milk tubes, and then the glycerin-broth added.

ARE AGED CULTURES NECESSARY?

In the beginning of this work, I was under the impression that it was essential to use only cultures at least six months old in order to transmute

the beads and granules of the bacilli of tuberculosis into the non-acid-fast and non-pathogenic cocci that I have described. I now know that the transmutation can be effected with young cultures of tubercle bacilli almost as readily as with old cultures. I have succeeded with human tubercle bacilli, bovine tubercle bacilli, and avian tubercle bacilli, all less than two weeks old. It is desirable, however, to have good generous growths of the tubercle bacilli on either the solid slants or in the flasks of glycerin-broth. With the very young cultures, there is sometimes, as I have already noted, an intermediate state between the erupted beads and granules of the tubercle bacilli and the fully developed darkly-staining cocci and diplococci. In this transition stage the granules of the tubercle bacilli first appear as pale tiny rods not longer than the average diameter of the granules or beads or cocci. These tiny rods look like two very tiny diplococci end to end. When, as sometimes occurs, there is a mixture of these tiny rods with cocci and the cocci have become of the screw-top variety, it is hard to resist the conclusion that the tiny rod is merely an elongation of one-half of the screw-top coccus. However that may be, I take greater interest in the securing of pure cultures of the cocci and diplococci than in permitting the tiny rod shapes to persist. The tiny rods, subcultured and placed at 37°, promptly transform themselves into the desired cocci and diplococci. Whereas, if the subcultures are kept at room temperature, the rods continue as rods, often grow as large as non-acid-fast tubercle bacilli; and, after a few weeks, many of the rods, especially those in the centre of clumps, become more or less acid-fast. Cultures of these rods killed and administered even by mouth to tuberculous patients give rise to strong tuberculin reactions and produce no beneficial effect on the patient. On the other hand, the coccal and diplococcal derivatives of the tubercle bacilli produce no tuberculin reaction and are often of great benefit to the tuberculous patient.

It has often seemed to me that the factor of greatest importance in producing the transmutation of tubercle bacilli into non-acid-fast, gram-positive harmless cocci and diplococci, was change of environment. I am no longer of that opinion.

Two of the best media at our disposal for culturing tubercle bacilli are sterile glycerin-broth and sterile milk. Growths of tubercle bacilli on these media grow rapidly, and grow acid-fast and retain well all their normal characters. Yet, when one adds to glycerin-broth growths of tubercle bacilli, a modicum of the supposedly inert substance, sterilized

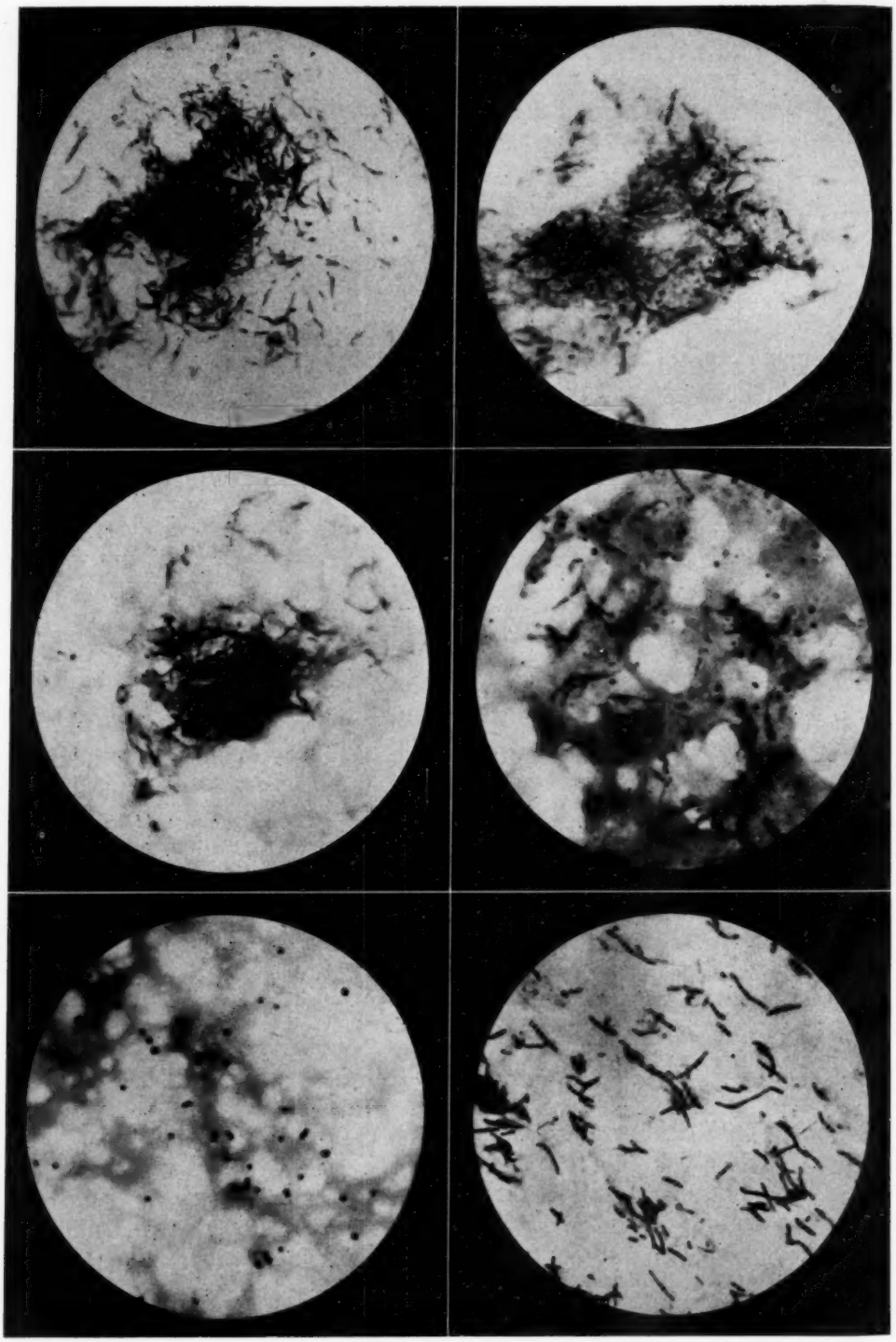


FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIG. 1. Human 37-4777. Pure culture as received from American Type Culture Collection. Typical tubercle bacilli, all acid-fast. Heavy dark granules in the bodies of the tubercle bacilli. × 900

FIG. 2. Human 37-4777. Same as fig. 1, after five days in milk-broth mixture. The bacilli are disintegrating; they have swollen and the granules are heavier. The acid-fast bacilli are enmeshed in a mass of non-acid-fast symplasm in which non-acid-fast indefinite granules can be seen. At this stage subcultures gave nothing but typical tubercle bacilli. × 900

FIG. 3. Human 37-4777. Same as fig. 2, two days later. The tubercle bacilli not in clumps are very pale pink and show marked disintegration and absence of granules. The clumps contain acid-fast disintegrating tubercle bacilli and much non-acid-fast symplasm. Typical non-acid-fast diplococci have begun to appear. Subculture gave scant growth of non-acid-fast cocci and diplococci, and occasionally some tubercle bacilli. × 900

FIG. 4. Human 37-4777. Same as fig. 3, two days later, or nine days after beginning of experiment. Milk mixture decolorizing and curdling. Many non-acid-fast cocci and diplococci. Tubercle bacilli still disintegrating. Subcultures gave luxuriant growth of non-acid-fast cocci. No tubercle bacilli grew at this time. × 900

FIG. 5. Human 37-4777. Same as fig. 4, five days later. Acid-fasts have all disappeared. Nothing remains but their transmuted offspring: non-acid-fast cocci and diplococci. × 900

FIG. 6. Human tubercle bacilli from pleural fluid. Subculture on glycerin-agar, four months old. All acid-fast bacilli with only a few granules. × 900

milk, the tubercle bacilli surrender most of their normal characters, and become non-acid-fast cocci and diplococci.

I still believe that the change of environment has much to do with many of the transmutations; but there must be something else involved, probably more important than change of environment. When using in this experiment only ordinary tubercle bacilli that, as everybody knows, will not vegetate unless they are provided with a temperature of 37°C. or thereabouts, it is easy to conceive that when supplied with so highly nutritious a food as a mixture of glycerin-broth and milk, and, at the same time, kept immersed in this food at a much lower temperature than is necessary for their multiplication, the vital spark that they contain, though unable to reproduce their kind, will be stirred into activity; and soon we shall find in our flasks and tubes an elongation and thickening of the bodies of the bacilli, and a development in these bodies of the familiar granules and polar beads; and, after a few days or weeks, these granules and beads will be extruded from the bacilli. In the satisfying medium into which these granules are born, they begin to take on the form and activities of cocci and diplococci. Not needing a higher temperature than that in which they find themselves, the cocci and diplococci multiply very fast, produce an acid, harmless to themselves but usually destructive to the remaining tubercle bacilli.

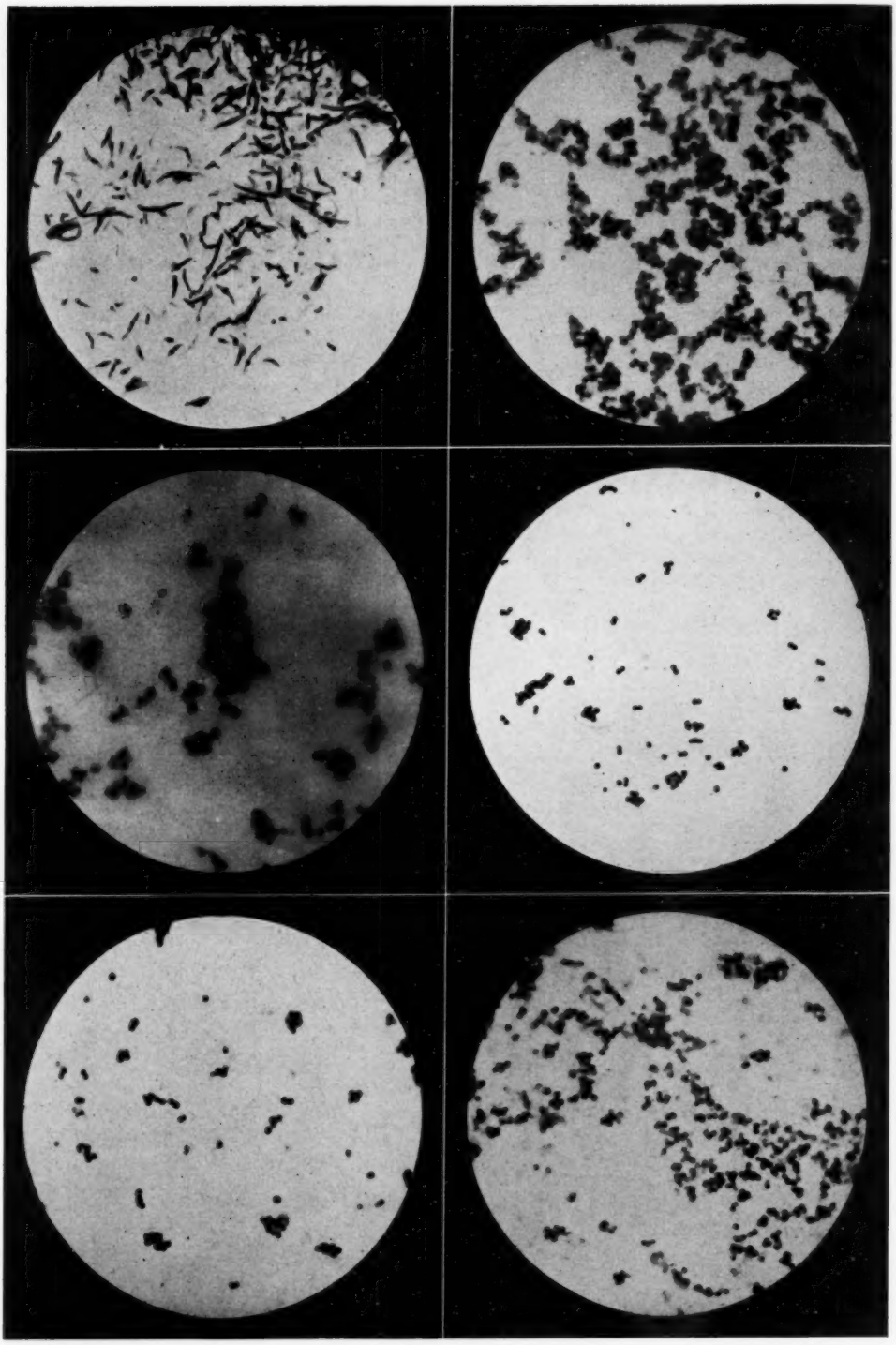


FIG. 7

FIG. 8

FIG. 9

FIG. 10

FIG. 11

FIG. 12

FIG. 7. Same as fig. 6, but after two weeks in milk-broth mixture at room temperature. Many bacilli have partially lost their acid-fastness. They show very heavy granules. × 900

FIG. 8. Same strain as figs. 6 & 7. Subculture on glycerin-agar of pH 5.2 from milk-broth mixture after eight weeks at room temperature. Note characteristic diploid arrangement occurring on acid media. The arrow points to two diplococci joined by a bacillary body, giving them the appearance of bacilli with polar beads. Glycerin-agar culture two days old. × 900

FIG. 9. Bovine 4363. Typical "screw top" appearance often assumed by coccal derivatives of tubercle bacilli. Subculture on glycerin-agar of pH 6.4 of coccals obtained by the milk-broth mixture from an original agar slant received from the American Type Culture Collection. × 1200

FIG. 10. Appearance of coccal derivatives of various strains of tubercle bacilli. Strain Shelton 8 on glycerin-broth. × 900

FIG. 11. Appearance of coccal derivatives of various strains of tubercle bacilli. Strain Avian Stors in milk broth. × 900

FIG. 12. Appearance of coccal derivatives of various strains of tubercle bacilli. Strain bovine 4363 (A. T. C. C.) on glycerin-agar. × 900

Yes, but that does not explain the transmutation into cocci and diplococci of the tubercle bacilli that, because they had been stored for long periods at room temperature in laboratories, have thus acquired the faculty of fast growing and of growing at temperatures of 20°C. or lower. These fast-growing forms of tubercle bacilli must feel the same urge in our flasks at room temperature that is felt by normal tubercle bacilli kept at 37°C. But, as a matter of fact, when subjected to our technique of immersion in milk and glycerin-broth, they too elongate, swell, display a body content of coccal granules and beads, and then drop these granules and beads and shrivel up, while the dropped granules and beads become cocci and diplococci, and proceed to lead a life of their own, independent of the bacilli from which they came and to the great detriment of these parent forms of the tuberculosis virus.

It is true that the task of securing pure cultures of the cocci and diplococci that come from the fast-growing tubercle bacilli is more difficult than is the task of culturing the coccal progeny of the orthodox or normal tubercle bacilli. Nevertheless, I have succeeded in the more difficult task with 6 different strains. Of four of these I have already spoken. The last two gave me considerable anxiety for a while. My associate, Dr. Campbell of Uncas-On-Thames, had sent to Chicago, to the John McCormack Collection, for a few cultures of bovine tubercle bacilli. He received several cultures on glycerin-agar. Among them were two bovine cultures marked *599* and *4363*. To the surprise of all of us we found that both of these strains *599* and *4363* were now "fast-

growers;" that is, they grew on all media like the timothy bacillus grew, and as much in 24 hours as orthodox tubercle bacilli would grow in 11 days. Both *599* and *4363* also grew luxuriantly at room temperature,

FIG. 13 FIG. 14

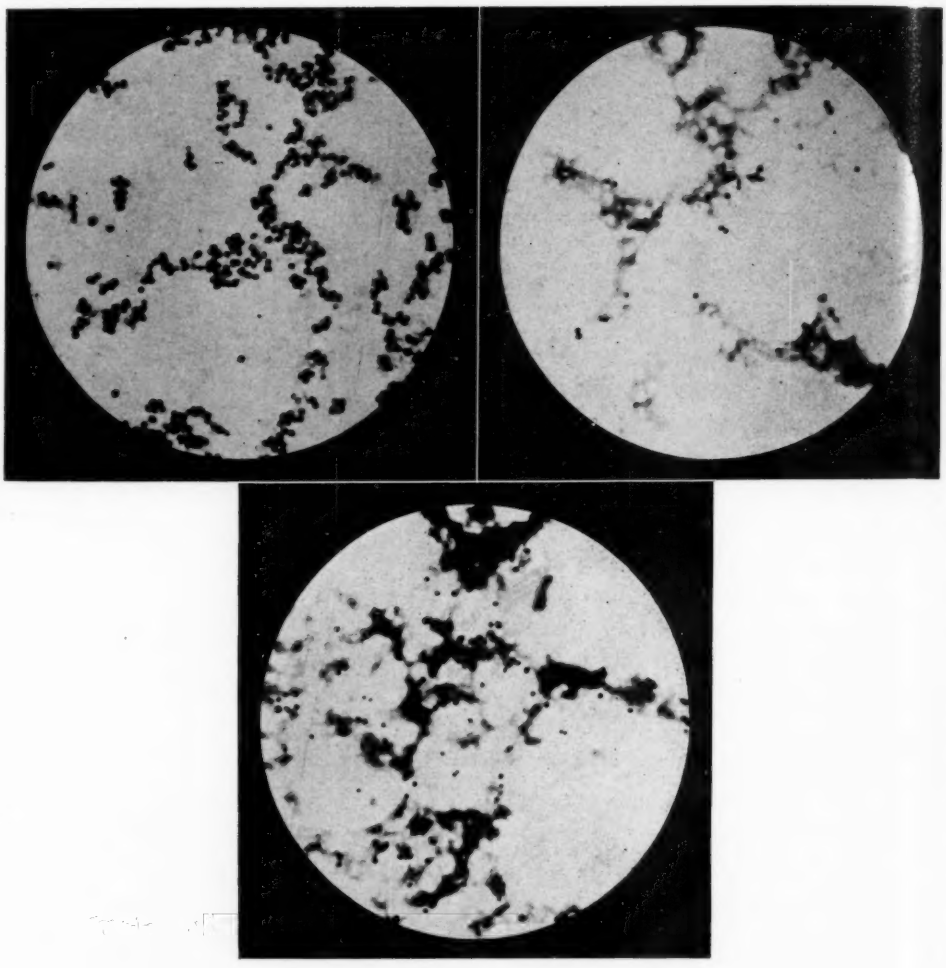


FIG. 15

FIG. 13. Appearance of coccal derivatives of various strains of tubercle bacilli. Strain human 37-4777 (A. T. C. C.) on glycerin-agar. × 900

FIG. 14. Appearance of coccal derivatives of various strains of tubercle bacilli. Strain human 37-4777 (A. T. C. C.) in litmus milk. × 900

FIG. 15. Appearance of coccal derivatives of various strains of tubercle bacilli. Strain bovine 4363 (A. T. C. C.) in litmus milk. × 900

and even in the original cultures from Chicago they had lost a good share of their acid-resistance. That is to say, clumps of half a dozen stained bacilli from the tube marked *4363* would consist of one bacillus brightly red and of medium length; 3 bacilli pale pink and several times as long as normal tubercle bacilli; and two bacilli, elongated, very pale blue or unstained. The *599* bacilli were shorter and of better staining but yet were "fast-growers."

I was very anxious to experiment with some proved strain of the bovine type; but, for the reasons already suggested, I hesitated about attacking the problem offered by these two abnormal cultures. However on September 24, I scraped off the growth on the two tubes from Chicago into a little glycerin-broth and poured the resulting emulsions into two flasks, each containing 250 cc. of glycerin-broth. After adding to each flask 50 to 60 cc. of litmus milk, as in the other experiments, I placed the flasks at room temperature in a dark cupboard. Not for many days was there any gross or microscopic change in the contents of the "4363" flask, except that, to my dismay, the long tubercle bacilli grew luxuriantly and formed a heavy pellicle on the surface of the content of the flask. These bacilli, however, were markedly more granular and black-beaded than the planted bacilli.

In the "599" flask, the non-acid-fast cocci and diplococci began to appear on September 29, and on the next day there commenced at the top of the medium a slight paling of the litmus blue. In this connection let me read my notes of three days. Remember the planting and the addition of the litmus milk occurred on September 24. Of the smears made from the "599" flask on September 28, my note book says: "Bovine 599. Immense, beaded, thoroughly acid-fast bacilli. No cocci and diplococci. None of the pale pink bacilli left."

The next day September 29, my note reads: "Bovine 599. Beautiful blue t.b. and beaded red t.b. and blue cocci and diplococci in clumps evidently developed from beads of beautifully black beaded red t.b. Striking picture."

One day later, September 30, my note reads: "Bovine 599. Beautiful clumps and loose masses of blue cocci and diplococci, sprinkled with red t.b. individual and in small masses. Most of the tubercle bacilli have parted with their black beads."

It will be seen that the change in the picture was startling, sudden and dramatic; but the task of getting pure cultures of these non-acid-fast cocci and diplococci by my usual technique was not so simply nor suddenly accomplished. Practically all the subcultures made from the

mother flask of "599" in the first days after the dramatic appearance of the cocci and diplococci in the flask, contained the elongated tubercle bacilli as well as the coccal forms and in about equal number even within 24 hours. At longer periods, especially on solid media, the bacilli grew often more luxuriantly than the cocci. I discovered however that some subcultures made from the mother flask on September 27, that is 24 hours before the acid of the cocci appeared in the flask and at a time when the microscope revealed only large bacilli apparently about to extrude their contained granules and beads, now contained a goodly proportion of fine blue cocci and diplococci. I quickly subcultured these growths of the September-27 tubes, and on second and third subculturings secured the pure cultures of the cocci and diplococci that I sought. No tubercle bacilli remained and I was able to add "599" cocci to the 17 other pure cultures of non-acid-fast cocci and diplococci that I have derived from various strains of tubercle bacilli.

Now to return to the flask containing "Bovine 4363". I made smears and subcultures from this flask almost every day for the next two weeks after the planting, but both the smears and the cultures showed only long granular and beaded tubercle bacilli. On October 12, the litmus in the flask being still unchanged, I planted from the unchanged media in the "4363" flask on to glycerin-broth and glycerin-agar and on the next day my notes of October 13 record with three exclamation marks as follows: "4363 glycerin-broth and milk of October 12th: blue cocci and diplococci and pink, red and blue long tubercle bacilli $\overline{aa}$!!!" and "4363 on Petroff of same date: All t.b. long, red, and pink."

Notes of October 15 disclose the fact that a subculture from the glycerin-broth culture of October 12, made October 14 on glycerin-agar, gave a pure culture of blue cocci and diplococci. Subcultures from this glycerin-agar culture of *4363* gave pure cultures of non-acid-fast cocci that have since grown true to form on many varieties of media. Therefore "Bovine 4363" stands in my collection as the eighteenth strain of tubercle bacilli to contribute non-acid-fast cocci and diplococci, and in proof of my claim that tubercle bacilli of any kind can be regularly and easily transmuted into culturable cocci and diplococci.

Thus far I have reported only on the transmuting of human and bovine tubercle bacilli into cocci and diplococci. There remains to be considered the avian type of tubercle bacilli. I have been experimenting with this type for many years with strains from Saranac Lake, from the Lister Institute in London and from the Phipps Institute in Philadelphia.

This last strain was a "fast-grower." In my work with the Phipps Institute cultures, I was never able to secure satisfactory non-acid-fast cocci or diplococci, but in those years I had not learned the simple technique for transmutation that I have described in this paper. From Lister Institute strains I secured very promising but very tender growths of small cocci and diplococci, but most of the subcultures either at room temperature or at 37° fused into symplasm, and from this symplasm I was not able to recover cultures of the cocci and diplococci, or of any bacterial forms.

Somewhat by accident I was more successful with the avian strain from Saranac Lake. My first efforts with this strain were to induce it to grow at room temperature. After long months of experimenting I succeeded, but the bacilli grew mostly non-acid-fast. I was fascinated with the thin dead white silky growth on the surface of glycerin-broth, both at room temperature and at 37°. One day in April, 1922, I took a flask of this Saranac Avian that had been growing non-acid-fast in the incubator and placed it at room temperature. On examining it a few days later I was astonished to find that it contained many large yeastoid masses of tiny rods and cocci mostly acid-fast. These masses planted in glycerinized liquid or solid media gave cultures of non-acid-fast cocci and diplococci and a queer non-acid-fast rod thicker than the tubercle bacillus and not granular. I found that I could cause these acid-fast rods to disappear in cultures grown at 37°, and I had thereafter pure cultures of non-acid-fast cocci and diplococci. I will not discuss them further at present because the purpose of this paper is to focus your attention on our new important and simple technique for transmuting tubercle bacilli into cocci and diplococci, a technique I had not learned at the time I was working on the Saranac Avian, or on the Lister Avian or on the Phipps Avian.

On October 10, 1933, I obtained from Dr. Campbell, of Norwich, a pure culture of avian tubercle bacilli isolated by Mr. Kieffer from a fowl sent by Storrs College to Uncas-On-Thames for study. With the transmuting technique already described, I have now secured pure cultures of cocci and diplococci from this strain of avian tubercle bacilli.

Last July, realizing the importance of acquainting the medical profession with my surprising results in changing acid-fast tubercle bacilli into culturable non-acid-fast harmless cocci and diplococci, it occurred to me that my own unsupported claims might fail of securing the attention that I hoped for, and that they deserved; and I decided that before

I made my results public, I would ask some of the prominent physicians among my associates in Connecticut's antituberculosis campaign to endeavor to corroborate my results in their own laboratories. Therefore, I told the treasured secrets of my work to Dr. Hugh B. Campbell, Superintendent of Uncas-on-Thames, to Dr. Cole B. Gibson, Superintendent of Undercliff Sanatorium at Meriden, and to Dr. Edward J. Lynch, Superintendent of Laurel Heights Sanatorium at Shelton, Connecticut. All three physicians eagerly accepted my offer and have willingly given time and effort to the work that I outlined for them. It so happened that Dr. Lynch had the best and largest supply of old cultures of tubercle bacilli on hand at the time. He was the first to report enthusiastically after two weeks that he had succeeded in breaking down a year-old culture of the H60 strain from Saranac Lake into beautiful cocci and diplococci, and a few days later that he had secured good pure cultures of these cocci and diplococci in glycerin-broth and on glycerin-agar. A few days later, he telephoned me that a second strain of tubercle bacilli isolated from one of his patients had become non-acid-fast cocci. Every week or two since he has notified me of the "popping of still another strain."

Dr. Gibson was next in his corroboration of my findings. With Dr. Gibson's corroborations I was greatly pleased, because members of his laboratory staff were frankly incredulous when they began the experiment. Dr. Campbell, at first hindered by some mold contamination of his cultures, has since succeeded with perfect results. I will ask these three physicians, Drs. Campbell, Gibson and Lynch to make themselves a short statement of their work in corroboration, and I know they will be anxious, as I am, to acknowledge the assistance rendered them by their technicians, Mr. Abraham Rosenman of the Shelton Sanatorium, Miss Mary Elizabeth English of the Meriden Sanatorium, and Mr. Jean Kieffer of the Norwich Sanatorium. And, of course, I am especially under obligation to Mr. Kieffer for all the photomicrographic work he has done to make my paper more intelligible to its readers.

I realize thoroughly that I am not the only worker who has seen cocci in old cultures of tubercle bacilli and who has speculated as to their origin and significance; but, like my work in the old years, their findings were accidental and their speculations as to the source of the discovered cocci were wild and unconvincing; and no formula, for enabling the laboratory workers of the world to reduce easily and invariably tubercle bacilli to cocci and diplococci, has ever been proposed by anybody anywhere.

The pH of my glycerin-broth has usually been as low as 6.4, but the

same results have been achieved with glycerin-broth of a pH of 7.2. In fact, a study of this matter by Mr. Kieffer shows that the cocci thrive well at all points between pH 6 and pH 7.4.

In preparing the litmus milk for these experiments it is best to have it well skimmed of cream before adding the litmus powder and before sterilization. In the course of this narrative, when I used the words "red" and "blue," I mean as probably all laboratory men realize, "acid-fast" and "non-acid-fast."

In the course of the experiment herein recorded, it will be understood that we have kept many controls: unplanted tubes and flasks of litmus milk and of glycerin-broth and of mixed glycerin-broth and litmus milk showed no development of coccal or other bacterial forms.

It should be understood that I have used in this experiment tubercle bacilli scraped from solid slants of glycerin-agar or Petroff's medium only because I had more cultures of tubercle bacilli on solid media than I had cultures of tubercle bacilli in flasks of liquid media. However as I have already noted, my first success was with a culture on glycerin-broth. All my co-workers have succeeded in developing the desired pure cultures of the blue cocci and diplococci from full-grown cultures of tubercle bacilli in flasks of glycerin-broth, by simply adding to these flasks 25 to 30 per cent as much litmus milk as there was glycerin-broth in the flask, and, as a rule, putting the flask in the dark and at room temperature, and keeping it there until its litmus blue color began to change to white or pink. I say "as a rule," because sometimes, when it is very young cultures of tubercle bacilli that we are testing and when the beaded and granular rods do not promptly give up their contained granules, subjecting the flask to a few hours of 37° will expedite the process of transmutation.

Of course the handiest stone available to the man or woman who desires to criticize such a paper as this or to deny the possibility of such findings as are here recorded is a cry of "Contamination!" We have realized that fact from the beginning and have prepared what we consider an impregnable defense against such stone-throwing: Contamination must mean contamination of the glycerin-broth, the litmus milk, the cotton plugs of the flasks and tubes, or exposure of the medium in the flasks to the air when removing the cotton plugs to make smears for microscopic study of the contents of the flasks, or during the pouring of the litmus milk into the glycerin-broth. It is not easy to persuade the skeptical that some foreign bacterial invader might not have entered our flasks when we pulled out the cotton plugs, no matter how tight the

plugs were and no matter how thoroughly we flamed the opened mouth of the flask before and after inserting the platinum loop or pouring the litmus milk. Nevertheless, the supposition that our results were due to such an accident must occur only to some very credulous person who can believe that the individuals of a certain unusual family of germs could have been waiting in my laboratory in New Haven, Dr. Lynch's laboratory in Shelton fifteen miles away, Dr. Gibson's laboratory in Meriden eighteen miles away, and in Dr. Campbell's laboratory at Norwich sixty-five miles away,—waiting for and prepared for the few seconds when they knew a certain specified flask of tubercle bacilli would be opened for sampling or pouring, and that there would therefore be an opportunity for them to enter these flasks, and not only to thrive among the contained tubercle bacilli but also to destroy most of these tubercle bacilli in the invaded flask. As to the sterility of the glycerin-broth and the litmus milk, there can be no question about that. These are tested every day. The freedom of the mixed milk and glycerin-broth from any other organism than tubercle-bacilli control tubes and flasks some kept at room temperature and some at 37° have proved it, and of course have also attested that the litmus powder was not a vehicle for contamination. The tubes and flasks used were all sterilized in the autoclave at 20 lbs. pressure, and when filled with media were again subjected to 20 lbs. pressure in the autoclaves. During the work on this matter for more than a year, I had a mold contamination in one flask and in three tubes and a spore-bearer contamination in one tube, but in all the hundreds of other tubes and flasks there was no sign of contamination.

The only bacteria the flasks and tubes contained were those described as resulting from the transmutation of the granules of tubercle bacilli into culturable cocci and diplococci. In some media there would be a predominance of cocci, in others of diplococci, in others of screw-tops; but transfers showed that the cocci, the diplococci and the screw-tops were merely three interchangeable forms of the same organism.

We have not as yet secured any convincing evidence from animal experiments that these cocci and diplococci have any preventive or curative effect on tuberculosis in guinea pigs or rabbits; but we have abundant evidence that these cocci and diplococci whether derived from avian, bovine or very pathogenic human tubercle bacilli, produce no harmful effect when injected into guinea pigs or rabbits. In itself, this is a very important matter if we are to consider any possible future therapeutic use of these cocci and diplococci derived from tubercle bacilli.

THE CLINICAL IMPROVEMENT OF PULMONARY TUBERCULOSIS BY MASSIVE ATELECTASIS

A Report of Six Cases[1]

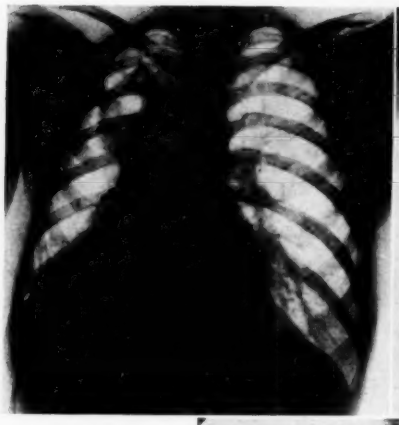
W. E. ADAMS AND J. J. SINGER

The association of massive atelectasis and pulmonary tuberculosis has been noted with increasing frequency during the past decade. Korol (1), Loeschke (2), Delafield and Prudden (3), Glenn (4), Singer (5), Hennell (6), Packard (7), Jacobaeus and Westmark (8), Gotterdam (9), and others believe that most of the so-called fibrotic lungs originate from the association of atelectasis with pulmonary tuberculosis. Not infrequently, marked clinical improvement in patients with pulmonary tuberculosis has been observed to occur concomitantly with the formation of massive atelectasis of the affected pulmonary tissue. This improvement had formerly been thought to be due to the production of fibrosis of the affected region. Scar-tissue contraction was held entirely responsible for the marked deviation of the mediastinal structures toward the affected side. The beneficial effects of scar-tissue formation in pulmonary tuberculosis are not to be denied. However, the evolution of this pulmonary fibrosis and its relation to bronchial stenosis with resultant atelectasis has only recently been investigated. It has been commonly believed that atelectasis (spontaneous) was an unfavorable complication of pulmonary tuberculosis (10) (11) (12) (13) (14). Good results have been reported following the treatment of this complication by artificial pneumothorax. In some cases of this kind the primary indication for this therapy was not signs of increasing toxicity, but symptoms resulting from displacement of the mediastinal structures.

Six cases of pulmonary tuberculosis whose clinical symptoms became markedly improved or alleviated concomitantly with the production of massive atelectasis of the affected part were observed by one of us (J. J. S.) and are being reported, as follows:

[1] From the Department of Surgery, the University of Chicago, and the Medical and Surgical Chest Service of the Barnes Hospital, St. Louis, Missouri.

FIG. 1a



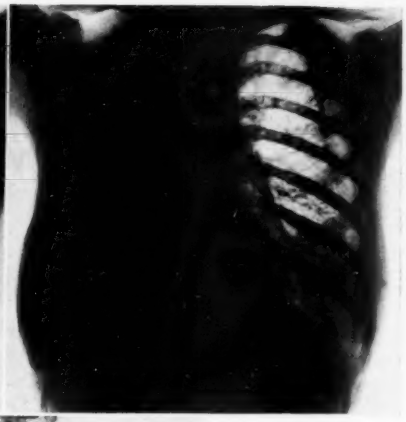


FIG. 1b

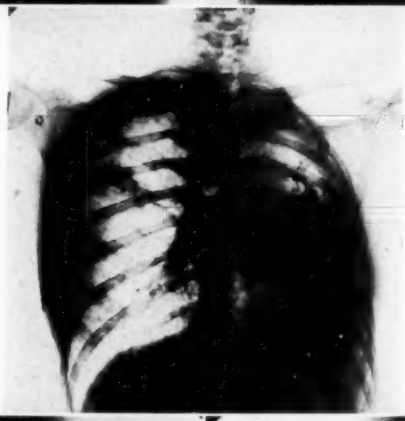
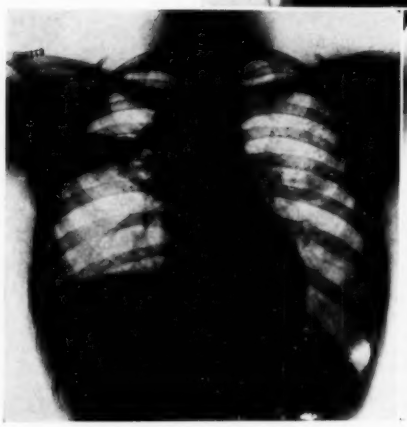


FIG. 2

FIG. 3a



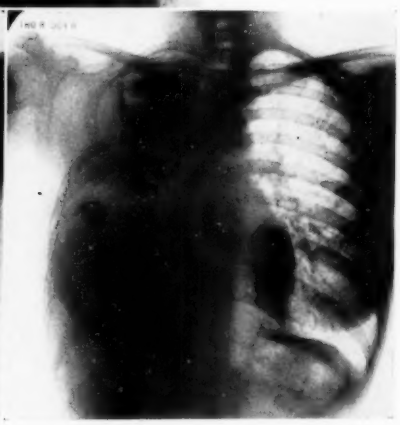


FIG. 3b

Fig. 1a. Case 1. Film of chest taken May 15, 1931, showing large cavity in right apex with partial pneumothorax. The right diaphragm is elevated and the heart is shifted to the right, suggesting some atelectasis and fibrosis of the right lung.

Fig. 1b. Case 1. Film of chest taken March 23, 1932. This reveals complete unilateral opacity on the right with the heart almost in the right chest.

Fig. 2. Case 2. Film of chest taken January 13, 1932, showing a large cavity in the left chest communicating with a bronchus as outlined by lipiodol. The trachea and heart are markedly deviated to the left. The entire left lung shows a marked increase in density.

Fig. 3a. Case 3. Film of chest taken May 11, 1931, revealing a large cavity in the right apex with a fluid level.

Fig. 3b. Case 3. Film of chest taken March 31, 1933, showing complete opacity of the right chest with marked shifting of the heart to the right.

FIG. 4

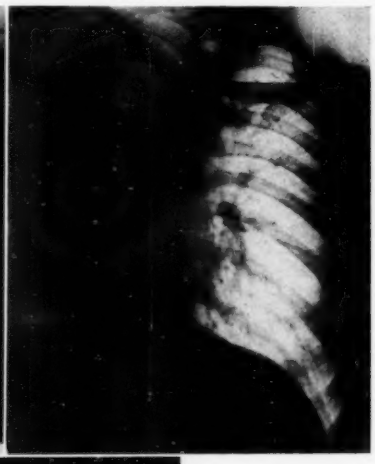


FIG. 5

FIG. 6

Fig. 4. Case 4. Film of chest taken October 29, 1916, showing complete opacity of the left chest obscuring the heart shadow. The heart and trachea are markedly deviated to the left and the diaphragm is very high. The shadows in the right apex are suggestive of a healed tuberculous lesion.

Fig. 5. Case 5. Film of chest taken May 2, 1930, following the introduction of iodized oil into the tracheobronchial tree. There is complete occlusion of all secondary bronchi on the left side with complete opacity of the left chest with some deviation of the heart to the left. The right lung shows compensatory emphysema.

Fig. 6. Case 6. Film of chest taken June 6, 1929, following introduction of iodized oil, revealed the trachea and main right bronchus dilated. There is complete opacity of the right lung with complete occlusion of the upper lobe bronchus, and partial occlusion of the middle and lower lobe bronchi on that side. The trachea and heart are markedly deviated toward the affected side. The left lung shows compensatory emphysema.

Cases

1: Miss A. H., 29, entered Barnes Hospital on April 9, 1931, with a history of chronic productive cough, malaise, slight lose of weight, afternoon fever and some laryngitis dating back to July, 1928. She was in a tuberculosis sanatorium for one year (November 1928 to 1929) during which time she became relieved of symptoms and returned home. In November 1930 she developed "flu" with haemoptysis of one cup full of blood. She has had a productive cough since that time and has experienced pain in the right chest for the past two weeks.

Physical examination and roentgen-ray revealed evidence of involvement of the entire right lung with a large cavity at the apex (figure 1a). The diaphragm was elevated and the heart shifted toward the right, suggesting some atelectasis and fibrosis in the right lung. A few râles were heard at the left base. Examination of the larynx revealed tuberculous involvement. Repeated sputum examinations revealed many tubercle bacilli. Pneumothorax treatment was begun April 14, 1931, and continued for three months. At the end of two months the patient developed a high fever which persisted until an avulsion of the phrenic nerve was done on July 14, 1931. Roentgen films of the chest showed the heart to be further deviated toward the right. With this change the temperature decreased and the patient improved clinically.

The patient was discharged, November 19, 1931, at which time physical signs and roentgen film revealed the heart and trachea markedly deviated to the right. She was observed from time to time and the lesion in the left lower lobe improved. Likewise, the laryngeal involvement became less on prolonged voice rest. Roentgen examination on March 31, 1932, disclosed complete unilateral opacity on the right, with the heart almost entirely in the right chest (see figure 1b). (Complete atelectasis. Marked clinical improvement.)

2: E. D., 27. This 27-year-old white girl's present illness began in June, 1929, with nonproductive cough, pain in the left chest and fever.

Her past history was never obtained satisfactorily in full detail, except that it is known that she had frequent colds with cough during the winter and that in 1920 she was examined at a well-known clinic as a neurosyphilitic suspect with the following report: neurological examination showed suggestive findings. The spinal fluid, however, was negative. The blood Wassermann on two occasions was strongly positive.

She entered Barnes Hospital on April 14, 1930, complaining of diarrhoea of several weeks' duration, fever, productive cough and marked loss of weight. Physical examination and roentgen ray revealed the trachea and the heart pulled into the left chest with the entire left lung involved. A large cavity connecting with a bronchus was clearly outlined by lipiodol (figure 2). Some

involvement in the right apex was also noted. Sputum and stool specimens revealed acid-fast bacilli. White blood count, 21,300 with 18 *stabs.*, 63 *segs.*, 10 *lymphs.*, 8 *monos.*, and one *eosinophile*; red blood count 4,000,000; haemoglobin 70 per cent; weight 88 lbs. A gastrointestinal roentgen-ray series showed an irritable bowel. Both the blood Wassermann and Kahn were 4-plus.

During her course in the hospital her temperature ranged between normal and 39°C., with periods of weeks when she would be afebrile. The atelectatic condition of her left lung progressed until at this time the left diaphragm was high, the trachea and heart were deviated well into the left chest, and a large cavity connecting with a bronchus was demonstrable with lipiodol.

In June, 1931, the patient had a severe haemoptysis, with subsequent fever and a spread to the right base which cleared in eight weeks. She received mercury inunctions and two courses of neoarsphenamine but her serological findings remained unchanged. The patch in her right upper lung field never changed and is considered as a scar from a previously active lesion.

She married in November, 1932, and continued to feel well except for a troublesome slightly productive cough; but she remained afebrile and weighed about 95 pounds. Her sputum remained positive for acid-fast organisms. The diarrhoea present in April, 1930, disappeared in three weeks without treatment and never recurred. She was clinically much improved until she developed a massive haemoptysis January 5, 1934, and died suddenly.

3: This patient's clinical course shows that massive atelectasis prolonged life.

A. D., age 27. History of frequent colds seven years ago with fever up to 103°. She saw a physician after about four months of the above condition, and the physician diagnosed pulmonary tuberculosis (right). She was at home in bed for two months when she had a haemorrhage (10 oz. +), and then decided to go to a sanatorium. She was there for four and one-quarter years, and gained some weight and strength, but had blood-streaked sputum at times. She was much improved when she left the sanatorium. Phrenicectomy was done one year before leaving the sanatorium after she had had pneumothorax treatments for two and one-half years. She also received three oleothorax treatments. In May, 1931, she came to Barnes Hospital to have oleothorax treatments continued. At that time the roentgen-ray and physical examination revealed evidence of a large cavity in the right apex (see figure 3a). She became worse, and had a haemorrhage in June, 1931. She remained in bed at home until September when she was admitted to Barnes Hospital. After two months she was discharged improved. Her condition remained stationary for the following six months, during which she was observed at the Chest Service of Barnes Hospital. In May, 1932, paraffin packing was attempted to close the cavity in the right upper lobe, but a spontaneous pneumothorax resulted. She was seen in the Chest Service on May 23, 1933, and

found to have improved much during the past three weeks. Roentgen-ray and physical signs showed an increasing atelectasis of the right lung with a shift of the heart to the right (see figure 3b). Improvement of her clinical condition followed the development of atelectasis of the right lung.

4: J. F. B., 45. Patient presented himself and asked for some medicine for a chronic nonproductive cough. He did not wish an examination. He had been a cornet player for many years (20 years). He was told he should have an examination to determine the nature of his condition.

On examination there was dulness over the entire left chest with areas of marked bronchial breathing, and with marked limitation of motion. The other lung presented signs of compensatory emphysema. Roentgen examination showed a massive shadow in the left chest obscuring the heart shadow, with the diaphragm very high and the trachea drawn far toward the left side. In the apex of the right lung there were shadows suggestive of a healed tuberculous lesion. *Diagnosis:* Bilateral pulmonary tuberculosis, with a healed right apical lesion and fibrosis of the entire left lung, now known to be massive atelectasis (see figure 4).

The patient was observed for several years following and was clinically well, playing his cornet daily in his professional capacity as a musician.

5: S. A., 34, was admitted to the Barnes Hospital May 1, 1930, with complaints of a productive cough for four months, and occasional dull pain in left chest. Following exposure last Christmas, the patient passed a few days of malaise, slight fever and chills, and developed bronchopneumonia in the left chest, followed by an effusion. The chest was aspirated January 24, and then repeatedly every 4 days, about two gallons of fluid being obtained. The fluid was replaced by air. Aspirations and air replacements were continued, with gradual decrease in the amount of fluid. The patient was hospitalized for six and one-half weeks, after which he returned home to be kept under observation and bed-rest. He had gained weight (had previously lost about thirty pounds) and his general appearance was improved. For the past three months he has had no fever above 99° although his pulse was rapid and there was some shortness of breath. Physical examination of the chest on April 24, 1930, revealed evidence of partial or massive collapse of the left lung with fluid. There was complete opacity of the left chest on fluoroscopy and the heart was drawn to the left. The right lung showed compensatory air content. The stomach air-bubble was slightly higher than normal and the left diaphragm moved very little. The roentgen-ray film of the chest following bronchography revealed complete occlusion of all secondary bronchi on the left side with complete unilateral opacity (see figure 5). On May 9, 1930, the physical signs of the chest showed an impaired percussion note over the entire left

chest, increased bronchovesicular breath sounds in the upper third of the left chest posteriorly with distant bronchial breathing in the lower two-thirds, absent tactile fremitus and increased whisper; no râles; compensatory breath-sounds throughout the right chest. *Heart:* Rate regular, sounds distant, no murmurs. Blood pressure 128/80.

Laboratory findings: Blood May 2, 1930: red blood count 4,840,000; white blood count 7,600; haemoglobin 75 per cent. The Wassermann and Kahn tests were negative. Report on aspirated pleural fluid: no growth. Repeated sputum examinations were negative for acid-fast bacilli.

May 2, 1930: An aspiration performed in the 6th interspace, axillary line: only about 5 cc. of a serous fluid with a suspicion of a sanguineous condition was obtained, but the fluid came with considerable difficulty through a very thick resistant pleura. Air was injected.

May 2, 1930: Lipiodol introduced following cocainization of the pharynx showed a wide main left bronchus with collapse of the smaller bronchi. No bronchi were seen beyond the mammary line. A complete, dense shadow around this area extended from the apex to the diaphragm. Here and there one could faintly see rarefaction. The right lung showed compensatory air content and some of the bronchi outlined by lipiodol were normal. This condition was not a true massive collapse.

May 12, 1930: Aspiration of about 30 cc. of fluid, followed by the introduction of lipiodol into the pleural cavity, showed many small fluid levels, and lipiodol with a fluid level. A tuberculin test gave a positive local, focal and general reaction.

The patient was discharged on May 15, 1930, with a diagnosis of atelectasis of the left upper lobe secondary to tuberculosis of that area.

A guinea-pig inoculation of pleural fluid was reported negative for tuberculosis on June 12, 1930.

It is not unlikely that the atelectasis of the upper lobe prevented a spread of tuberculous disease and thus was instrumental in its clinical improvement.

6: T. W., white man, 32 years of age, was admitted with symptoms of tuberculosis in the right lung. His sputum was positive for tubercle bacilli. Pneumothorax treatment had been given elsewhere. A massive pleural effusion developed later. Physical signs on admission revealed dulness throughout the right chest with bronchial breathing, but no râles. His general condition was good. Roentgen-ray examination, June 6, 1929, following the introduction of lipiodol, revealed the trachea and main right bronchus dilated. The upper-lobe bronchus was completely occluded, and the middle- and lower-lobe bronchi partially occluded. *Diagnosis:* Pulmonary tuberculosis with fibrosis and partial atelectasis of the right lung. The trachea and cardiac shadows were deviated toward the affected side, and the right diaphragm was elevated. The

left lung showed compensatory emphysema (see figure 6). A diagnostic thoracentesis revealed no fluid in the pleural cavity. *Impression:* Pulmonary tuberculosis with atelectasis of the right lung. The patient's sputum became negative and his cough disappeared on conservative treatment. He was observed two years later and appeared clinically well. At that time the beneficial results were thought to have been due to fibrosis alone, whereas now it is felt that atelectasis played the major rôle.

EXPERIMENTAL ATELECTASIS OF THE LUNG

A means of investigating the effect of atelectasis on pulmonary tuberculosis was presented by one of us (W. E. A.) in the development of a safe and reliable method for producing massive atelectasis in animals, introduced a few years ago (15) (16). This procedure consisted of cauterization of the bronchial mucosa with a 35 per cent solution of silver nitrate applied through a bronchoscope. About two weeks subsequent to cauterization complete stenosis of the bronchial lumen occurred. This was routinely accompanied by massive atelectasis of the lung. Microscopic studies were made of atelectatic areas in various stages of chronicity which had been produced by the above method. Marked changes in vascularity of the tissue were noted (17). During the early weeks the capillaries appeared to be dilated and tortuous. After a few months had elapsed, sections of the atelectatic tissue revealed many dilated spaces filled with blood, haemangiomatous in appearance. By comparing microscopic sections taken before and after injection of the animal with a solution of india-ink according to the technique of Coryllos and Bierbaum (18), the vascular changes were found to consist of a marked passive congestion. Some of the collapsed tissue was reinflated *in vivo*. Microscopic sections taken before and after reinflation, with and without injection of india-ink, were compared. The dilated spaces filled with blood were found to be alveoli through which blood was flowing. A complete report of these experiments may be found elsewhere (19).

Thus, by this method of producing collapse, we obtained a passive congestion of the obstructed pulmonary tissue and absolute rest of the part, more complete perhaps than by any other known method. With this method of producing atelectasis available, the effect of atelectasis on pulmonary tuberculosis, produced experimentally, has been recently investigated. A complete report of this investigation may be found elsewhere (20) and only a brief summary of the results will be given here.

We were very fortunate in being able to produce tuberculous lesions

in dogs with tubercle bacilli (H119*) with routine regularity. The tuberculous lesions in lungs were produced by three methods, namely, the haematogenous route, the bronchogenic route and by direct inoculation. In the haematogenous group of 26 dogs, a miliary type of pulmonary tuberculosis was obtained and was confined to one lung in 8 dogs by injecting a coarse suspension of the organism into the left pulmonary artery. Massive atelectasis of the affected side in the unilateral cases, and of one or two lobes in the bilateral cases was produced two to six weeks after infection. In 8 dogs, direct inoculation of two or three lobes through a thoracotomy opening, using a suspension of tubercle bacilli in lipiodol, produced gross pulmonary excavations which were collapsed three to eight weeks after infection. Twenty-six dogs were used in the bronchogenic series, eighteen of which were unilobar. One goat was also added to this latter series. A lipiodol suspension of the bacilli was introduced into the finer air-passages through a bronchoscope. Gross cavities, 2 to 4 cm. in diameter, were produced with routine regularity by this method. Atelectasis of the pulmonary lobes containing these cavities was produced three weeks to five months following infection, while the lesions were still demonstrable by roentgen ray.

Results following artificial atelectasis: The animals were killed from a few weeks to twelve months after the atelectasis developed and the various stages of the collapse of the lung were studied. Uniform beneficial results from the collapse were noted in all three series of experiments.

In the haematogenously infected series of dogs a marked contrast between the atelectatic and normally inflated lobes was apparent. Whereas the inflated lobes were studded with tubercles, the collapsed lobes showed very few or no gross tubercles. Microscopic sections presented very few minute tubercles in the collapsed tissue. Sections stained for tubercle bacilli revealed very few organisms,—sometimes as low as one bacillus in several fields in the collapsed tissue,—whereas inflated lung tissue exhibited almost countless numbers.

Likewise, in lesions produced by direct inoculation there was evidence of healing after atelectasis had been produced by bronchial occlusion. A longer time was necessary for changes showing any beneficial results due to the magnitude of the lesion before collapse was produced. Tubercle bacilli (by stained sections) disappeared earlier in lesions which were collapsed than in control lesions of the same animal.

In the bronchogenic-infected series, tuberculous cavities became completely obliterated and were replaced by scar-tissue following collapse

of that lobe by bronchial occlusion. The tubercle bacilli disappeared from these lesions and a considerable amount of calcium deposition was noted. No animal died as a result of closure of a bronchus draining a tuberculous cavity. Some difficulty was encountered in attempting to close bronchi through which there was a considerable amount of drainage from a large cavity.

The routine regularity of production of tuberculous lesions by the three methods used was of very great importance. The effect of collapse of these lesions could be extremely well controlled and evaluated.

The marked contrast between the atelectatic and inflated lobes in the bilateral haematogenous series a few weeks following infection was most surprising. This was especially true when one considered the fact that the advance of tuberculosis in the inflated lobes and the healing of the lesions in the collapsed lobes were taking place simultaneously in the same animal. In a similar manner, in the unilateral haematogenous group the marked contrast between the collapsed, infected left lung and the normally inflated, noninfected right lung was very outstanding. The resulting infection in the noninfected right lung was due to organisms circulating through the injected left lung back to the heart and through the general circulation before finally arriving in the right lung. The injected left lung receiving the bulk of the infection was able to combat the infective organisms by means of the atelectasis produced.

In producing massive atelectasis by the methods described, gross mechanical and chemical (19) changes were brought about in the collapsed pulmonary tissue. The lung was placed in an absolutely functionless state,—a state which we have learned is a fundamental principle to be observed in the treatment of tuberculosis. A marked passive congestion of the pulmonary tissue was a constant occurrence. With this there was a marked increase in carbon dioxide and a reduction of oxygen to a very low level in the collapsed pulmonary tissue. Which of these factors plays a major rôle in the healing of pulmonary tuberculosis is still a debatable question.

DISCUSSION

The spontaneous development of atelectasis in pulmonary tuberculosis is well illustrated in all of the reported cases. In cases 1, 2 and 3, with the development of massive atelectasis of the more involved lung, the patients were able to combat the disease to such an extent that they were clinically improved, although occasionally raising positive sputum.

The fourth and sixth cases illustrate patients in which, following the development of massive atelectasis of the diseased lung, they were apparently cured of the disease. Although in case 5, the diagnosis was questionable, the history and physical findings suggest very strongly that this too was a case of pulmonary tuberculosis with massive atelectasis playing a major rôle in the improvement of the patient.

The striking clinical improvement in cases of pulmonary tuberculosis occurring concomitantly with the production of massive atelectasis may be explained in the light of the experiments above described. Pulmonary lesions produced experimentally in dogs were shown to have become markedly improved or healed by the production of massive collapse of the affected part. It is even more surprising that this should have occurred in one part of the lung while the animal was dying from a lesion in an adjacent portion of the lung. In order to collapse a tuberculous cavity in the animal it was necessary to produce complete occlusion of the main bronchus of the entire lobe, thus completely cutting off the only avenue for drainage of that lobe. With these facts in mind the conclusion may be drawn that one or both of two factors are responsible for the results obtained, namely, complete rest of the part and chemical changes produced in the collapsed pulmonary tissue. From a study of these cases and the above-described experiments it is impossible to determine which of the two factors plays the major rôle. It has been conclusively demonstrated that changes in the oxygen and carbon-dioxide percentages in the lung are of vital importance to the life and growth of the tubercle bacillus (21) (22) (23) (24) (25). These percentages may be changed experimentally by obstruction of bronchi with resulting atelectasis.

SUMMARY AND CONCLUSIONS

Massive atelectasis is occasionally associated with pulmonary tuberculosis and may be the major factor in determining whether an arrest or cure of the condition results. This atelectasis is readily demonstrable when involving an entire lobe or lung, but probably occurs in many more cases than is clearly demonstrable. Improvement in clinical symptoms concomitant with the development of atelectasis has been repeatedly observed. The amount of improvement is partially dependent upon the resistance of the patient. With this clinical improvement in cases of pulmonary tuberculosis the major symptoms observed may be those of secondary bronchiectasis as is shown in one of the reported cases. Secondary infection of pulmonary tuberculous lesions

may prevent production of massive atelectasis in a certain percentage of cases. The healing of the tuberculous lesions is due to rest of the part and changes brought about in the chemistry of the obstructed part. Decrease in oxygen and increase in carbon-dioxide content are the more important of these chemical changes, the former probably playing the more important rôle.

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EXTRAPLEURAL THORACOPLASTY IN PULMONARY TUBERCULOSIS

Results in a Series of 50 Cases

JEROME HEAD

From July, 1931, to June, 1933, I was surgeon to the Chicago Municipal Tuberculosis Sanitarium and during that time my assistants, Dr. Davison and Dr. Rappaport, and I performed 50 thoracoplasties. It has seemed advisable to report this group separately because it presents a picture of the operation as it is being used to-day and because it permits a comparison between the old Wilms-Sauerbruch operation and a newer and more radical thoracoplasty which was developed and adopted during this period, and also between partial and complete thoracoplasties.

For some time it has become increasingly apparent that the Wilms-Sauerbruch posterior thoracoplasty too frequently provides insufficient collapse and that too frequently the persistence of patent cavities and positive sputum necessitates reoperation. This is not a new idea, for early in the history of the operation Brauer stated that for thoracoplasty to be uniformly successful the collapse afforded must approach that of a satisfactory pneumothorax, and Wilms's original plan for the paravertebral operation included resection of the cartilages anteriorly. In 1932 John Alexander advised this addition for patients with large apical cavities. At his suggestion I then started using it and found that it not only improved the collapse materially but added little to the shock of the procedure. For these reasons I adopted it as a routine in all cases and later extended it to include the removal of the remaining segments of the upper three or four ribs. It has seemed to me that the slight accessory operation was amply justified by the assurance of a complete compression.

In selecting patients for operation the old standards were largely abandoned. These demanded that the patient be in good general condition, that the disease be chronic and productive and that the opposite

lung be free from active disease. Such cases are the ideal, but, if one waits for each to fulfill these requirements, he will operate rarely, will

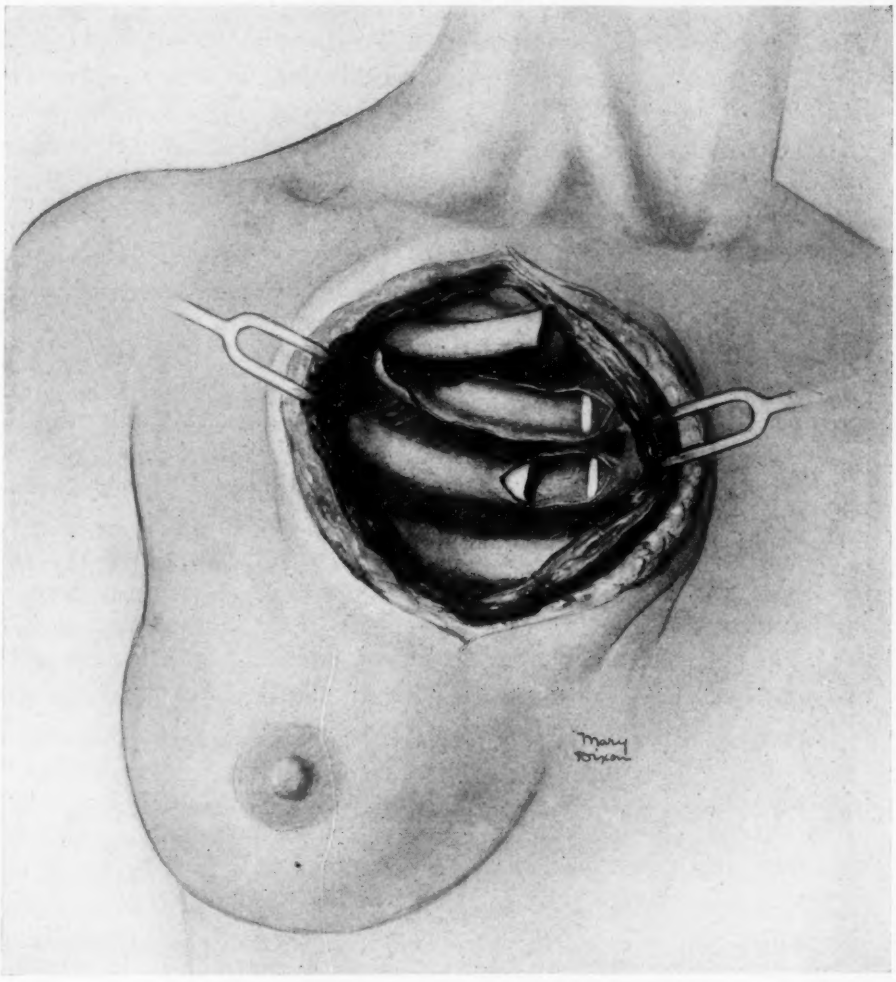

FIG. 1. Drawing, illustrating the anterior supplementary operation, with resection of the upper four costal cartilages, or of these and the remaining segments of the corresponding ribs.

watch many die who might have been saved, and will see many others waste valuable years and finally come to operation so damaged by sepsis that arrest of the tuberculosis will fail to restore them to useful activity.

In this group thoracoplasty was advised as soon as it became reasonably certain, judging by experience and close observation, that other measures would not suffice. Patients with large cavities which could not be collapsed by pneumothorax and which experience had taught rarely closed after phrenicectomy were submitted early to the operation as were those with soft, progressing disease which in spite of other measures continued to progress.

In many such cases delay means almost certain death either from extension to the opposite lung or from enteritis. I do not mean that the operation was performed upon any patient who had a fair or even a slight chance of recovering without it. I do mean that it was not regarded as a last and desperate resort to be used only when the patient had weathered every risk of the disease and had settled down to the even course of the chronic fibroid.

It is my belief that this conception of the indications is largely responsible for the noted improvement in the results and that only when it is so used will the operation play the rôle that it can and should play, —an operation with relatively wide indications (especially the local thoracoplasty) with a mortality of one or two per cent.

In speaking of the indications I should add that no attempt was made to avoid risks. All in whom the operation was at all indicated were advised to submit to it. Two were over fifty years old, two had cavities in the opposite lung, one had had a contralateral pneumothorax for two years, most had arrested or quiescent disease, and many some active disease in the opposite lung. Enteritis and laryngitis were considered contraindications only when severe. At first, in an attempt to rule out some of the worse risks, very careful clinical studies were made to detect amyloidosis, myocardial damage and low vital capacity. These tests were soon either abandoned or disregarded on the basis that if a person needed a thoracoplasty he had better take the chance regardless of any increased danger. Disease in the opposite lung and severe extrapulmonary complications emerged as the only contraindications; the former is the most important and difficult consideration. Proper handling of it can come only from long experience with the operation combined with a thorough knowledge of tuberculosis. When there is active disease in the opposite lung it is very difficult to know whether it is best to proceed with the operation, wait for further resolution or hardening, or resort to preliminary contralateral pneumothorax.

The general results are as follows:

Condition	*Number of cases*	*Per cent*
Arrested	19	38
Apparently arrested	9	18
Sputum negative and positive	9	18
Improved	8	16
Unimproved	1	2
Worse	0	0
Operative death	1	2
Late death	3	6
	50	100

Combining the arrested with the apparently arrested and the improved with the greatly improved gives the following figures:

Condition	*Number of cases*	*Per cent*
Arrested or apparently arrested	28	56
Improved or greatly improved	17	34
Unimproved	1	2
Worse	0	0
Dead	4	8
	50	100

Those listed as having negative and positive sputum are clinically cured save that on an occasional monthly examination they show a rare bacillus. All have little or no cough, little sputum, no fever and no disease in the opposite lung. In each the prognosis for complete recovery is excellent.

Those listed as improved have persistently positive sputum either from an incomplete collapse or from preëxistent disease in the opposite lung. There were no instances of spill into the contralateral side or of exacerbation of disease already present. Of the eight so listed five had imperfect collapses and no contralateral disease. One of these had had a supplementary pack, one an unsuccessful Caspar operation, and two of the others were scheduled for reoperation at the time that I resigned.

The single patient listed as unimproved is a man fifty years old with marked emphysema and bilateral apical cavities which were treated by

paraffin packs. One of the packs extruded and when it was removed a thoracoplasty was substituted. He was not made worse.

The patient who died following the operation developed considerable paradoxical respiration and refused to aid herself by lying on the affected side. After a few stormy days she improved, and by the tenth day her temperature, pulse and respiration were normal. On this day she was taken suddenly with severe dyspnoea, pain and cyanosis, and died five minutes after their onset. No autopsy was obtained. The clinical diagnosis was embolism of the pulmonary artery.

All of the late deaths were in spite of, rather than because of, the operation. One who had been improved died of acute pancreatitis two years after the operation. Another who was an extremely bad risk, having a high fever, extensive disease in the opposite lung and definite enteritis, was markedly improved by the operation. Her temperature became normal and she continued to gain for several months. Her temperature then rose, she became increasingly dyspnoeic, and finally succumbed. Autopsy showed that the opposite lung was almost completely collapsed by a large pleural effusion. Had this been recognized and aspirated, death surely would have been delayed and recovery might have followed. The third patient was apparently cured, having had a negative sputum, no cough and no fever since the operation. At the end of three months he became demented and was transferred to the psychopathic hospital. Word was received that he died shortly afterward, probably of cerebral tuberculosis. The one death from pulmonary embolism was the only one which can in any way be attributed to the operation.

While early results from thoracoplasty are inconclusive there being for years in any series a constant shifting from one classification to another, comparative results within a series are of definite value. As has already been said this group is reported because it presents a picture of the operation as it is being used to-day and, what is more important, because it affords a comparison between different types of operation. It includes 20 instances of partial upper thoracoplasty, and twenty-eight complete. In 14 cases only the posterior operation was used, in thirty-four this was supplemented either by resection of segments of the upper three or four cartilages (16 cases) or of these plus the remaining segments of the ribs (15 cases). The results in these various groups are shown in tables 1, 2 and 3.

TABLE 1

OPERATION	NUMBER OF CASES	SPUTUM NEGATIVE				SPUTUM NEGATIVE AND POSITIVE		IMPROVED		UNIMPROVED		WORSE		OPERATIVE DEATH		LATE DEATH	
		6 mo.		3 mo.													
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Posterior upper	5	1	20	1	20	1	20			1	20					1	20
Anterior and posterior upper	15	6	40	3	20	3	20	3	20								
Posterior complete	9	5	55	0	0	1	11	2	23					1	11		
Anterior and posterior complete	19	6	31.6	5	28.4	4	21	2	10							2	11
Reoperations	2	1	50	0	0	0	0	1	50								
Total	50	19	38	9	18	9	18	8	16					1	2	3	6
		28		56%													

TABLE 2

OPERATION	NUMBER OF OPERATIONS	ARRESTED OR APPARENTLY ARRESTED		IMPROVED OR GREATLY IMPROVED		UNIMPROVED		WORSE		DEAD	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Posterior operation	14	7	50	4	29	1	7			2	14
Anterior and posterior operation	34	20	60	12	35					2	5

TABLE 3

OPERATION	ARRESTED OR APPARENTLY ARRESTED	IMPROVED OR GREATLY IMPROVED	UNIMPROVED	DEAD
	per cent	*per cent*	*per cent*	*per cent*
Posterior upper	40	20	20	20
Anterior and posterior upper	60	40		
Posterior complete	55	33		11
Anterior and posterior complete	60	31.6		9
Reoperations	50	50	0	0

Although the number of cases in each group is small, these figures are of great interest. They suggest, first, that the results from partial thoracoplasty when supplemented by the anterior operation compare

favorably with those from the complete operation; second, that the complete posterior operation is slightly more effective when supplemented by the anterior procedure; and third, that the simple posterior partial operation is much less effective than when combined with the anterior.

The relatively higher percentage of arrested cases in the group treated by the complete posterior operation is almost certain to be accounted for on the basis that these were the first cases operated upon and that a longer time has intervened for healing to become complete.

In so far as the statistics suggest that the results are favorable in direct proportion to the completeness of the collapse, they bear out what experience with collapse therapy has shown must and will be the case.

SUMMARY AND CONCLUSIONS

1. The early results are reported in a series of 50 thoracoplasties in which different types of operation were used.

2. Fifty-six per cent are arrested or apparently arrested, 18 per cent are markedly improved and with a favorable prognosis, 18 per cent are improved, 2 per cent are unimproved, 2 per cent died from the operation, and 6 per cent died later of causes unconnected with the procedure.

3. These favorable results are attributed to freer and earlier use of the operation and to the fact that in every case the collapse was rendered exceptionally complete.

4. The results in the different groups of cases were in proportion to the completeness of the collapse of the diseased lung area.

5. It is suggested that if thoracoplasty is used at the proper time and if a complete collapse of the disease is obtained, the indications for the operation will be considerably extended and the results markedly improved.

THORACOPLASTY

A Report of 50 Consecutive Cases[1]

PAUL D. CRIMM, J. W. STRAYER AND CLARENCE S. BAKER

This report presents a series of 92 operations on 50 consecutive patients with pulmonary tuberculosis. The operative mortality was nil. Prior to operation all cases were hospitalized until each one became a fair operative risk. If a poor risk, the patient was treated conservatively until his general condition warranted operative consideration.

PREOPERATIVE PROCEDURE

Bilateral disease was not considered a contraindication, dependent, of course, upon the extent and character of the lesions in the contralateral lung. Approximately two weeks prior to the operation, viosterol 250 D, (1.5 cc.), *per diem* was administered. Tincture of digitalis (1 cc.) twice daily, with a total dose of 15 to 20 cc., was given during this period. At five o'clock on the day prior to the operation, the patient was allowed light nourishment. On the morning of operation S.S. enemata were given until clear. All liquids were withheld after six A.M.

The day before operation, the operative site was shaved and scrubbed, and tincture of merthiolate applied, followed with a sterile dressing. This was repeated three hours before the patient was prepared in the surgery.

Postural drainage was urged for patients with large cavities. A few of the cases were not operated upon until one or two o'clock in the afternoon in order to effect drainage. It is also important to keep the nasal sinuses open. In our climate we seldom operate upon a case that does not have a low-grade sinusitis.

As much air or fluid as practicable was removed from the pleural cavity in pneumothorax cases; likewise, a pyopneumothorax case was drained before and after operation to effect a satisfactory collapse. Vital capacities were recorded before and after each operation. A few cases were operated upon successfully whose vital capacity ranged between 800 and 1000 cc.

[1] From the Boehne Tuberculosis Hospital, Evansville, Indiana.

It is not desirable to give a large dose of a hypnotic. We find that pentobarbital or sodium amytal (gr. 1 ss.) two hours prior to the operation, followed by morphine (gr. $\frac{1}{4}$), one hour before operation, is sufficient to hold the patient nicely without lowering his blood-pressure. The administration of too much hypnotic tends to supplement surgical shock.

ANAESTHESIA

In this series of cases all operations were performed under nitrous-oxide-oxygen anaesthesia. By this we do not mean nitrous-oxide-ether, since ether was not used in a single case. Neither did we add any other synergist such as chloroform or paraldehyde.

All inductions were quiet and easy, without excitement or feeling of suffocation. The patient was always ready for incision within five minutes. There was never any necessity for removing the mask which would interrupt an even stage of anaesthesia. Anoxaemia and cyanosis are not permitted, since an ample percentage of oxygen was employed to maintain a good color of the blood and tissues.

The tidal respiration was always measured after the patient was anaesthetized and re-breathing to one-half the tidal capacity was practised; that is, if the tidal capacity measured 600 cc. per breath, the re-breather was set to allow 300 cc. of the exhaled gas to be taken back at each respiration. The remaining 300 cc. of tidal capacity was therefore filled with fresh gas from the mixing chamber of the apparatus at each breath.

One of the chief reasons for our results is the ability to maintain sufficient anaesthesia with nitrous oxide without ether. The respiratory passages are kept dry during the operation. Nitrous-oxide-ether anaesthesia, which is extensively practised, has little or no advantage over straight ether anaesthesia.

We have considered intratracheal anaesthesia; but the time necessary for introducing the tube into the trachea, which necessitates the use of a laryngoscope and often ether anaesthesia, is nearly sufficient for our usual method of anaesthesia with completion of the operation.

OPERATIVE TECHNIQUE

Our technique varies little from that generally employed by those doing chest surgery. We make a crescentic incision around the scapula usually long and low enough to permit a second or third stage through the lower part of the same incision. This eliminates a second and lower

incision which in healing often leaves a wide scar due to aseptic necrosis along the lateral margin of the wound. Although we use a knife to incise the skin and underlying adipose tissue, a high-frequency current is used to incise all muscles and to split the periosteum. This procedure together with the use of viosterol reduces bleeding to an ideal minimum. Each bleeding point is clamped. It is seldom necessary to tie blood-vessels. Permitting the haemostats to remain on vessels until ready for closure lends speed to the operation. The fact that the patient's wound is bandaged tightly with a large heavy dressing, and that he lies on the operated side or on his back, controls any excessive oozing which may result from the lack of more meticulous haemostasis.

The time element is extremely important in this operation. Prolonged anaesthesia, especially local, adds greatly to the shock of the patient. Our initial stage generally consists of the removal of the first five sections of ribs, if a total thoracoplasty is the ultimate goal. The operative time for this stage is approximately thirty minutes. Subsequent stages require fifteen or twenty minutes.

In doing the first stage we find little difference in the patient's condition, whether five or three sections of ribs are removed. If the entire length of the 2nd, 3rd, 4th and 5th ribs should be removed, we believe it easier on the patient to remove three to five sections of ribs anteriorly at the initial operation. The patient recovers rapidly from this anterior operation and can again be operated upon in two weeks, at which time corresponding sections of ribs posteriorly can be excised. Then, if a longer period is desired following the posterior operation, one can wait indefinitely on the subsequent stage, providing an anterior stage has been completed. We have not found it necessary to remove the first rib in its entirety. A section of the first rib from the vertebral spine to a point just beyond the scalene tubercle has given good results.

In our cases there was no more interference with the scapula and the proximate unexcised rib by removing four, five and six sections of ribs, since the shape of the operated thoracic cage and its relation to the length of the scapula vary with the individual.

Chromium No. 2 was used for closing the muscles, and a continuous braided black silk suture was used in closing the skin.

We feel that the patient is less toxic for having drainage posteriorly than having the wound closed tightly. However in the anterior operation, the wound is closed tightly. In this operation a crescentic incision is started from the 2nd rib encircling the mammary gland medially.

A binder is tightly pinned around the chest over the dressing. The patients wear these binders three months after the last, and always between operations. Three to five weeks are permitted to pass before subsequent posterior operations are considered. A satisfactory collapse has been obtained when two to four months have intervened between operations.

POSTOPERATIVE CARE

In this series of cases blood transfusion was required in only one case postoperatively. A second case was given a blood transfusion prior to a second-stage operation. Most of our patients exhibited signs of very mild shock, the systolic blood-pressure usually dropping to between 100 and 90 mm. Hg. Only two showed an alarming amount of shock and these recovered within a few hours. Two thousand cubic centimetres of saline solution by hypodermoclysis are given immediately after each operation. This routine permits the patient to recover quickly and assists in restoring the blood-pressure. It also minimizes nausea and thirst.

For pain, morphine (gr. $\frac{1}{6}$ to $\frac{1}{4}$) was given every four to six hours. By moving the patient at times and by the use of ammonium chloride we have been able to assist the patient in raising tenacious sputum.

A cigarette drain is removed forty hours after the operation. The patients lie on the operated side as much as possible although some patients are more comfortable on their back. Fluids are given as soon as tolerated.

In our experience a continuous braided silk suture in the skin was the least objectionable of any form of closure. There is, however, a decided tendency for the suture to bury itself and to produce a rather severe reaction unless removed early. We therefore routinely removed the stitches on the fifth day and secured the wound with three butterfly straps.

Nose drops of metaphedrin followed by neo-silvol were given two to three times daily postoperatively, in order to prevent sinus and middle-ear infections.

In cases with healed intestinal tuberculosis, as evidenced by X-ray, it is advisable to place the patient on an ulcer diet for a few weeks following operation. The equilibrium between the gut wall and any pathogenic organisms present may be disturbed by the operation.

The patient is allowed to sit up in bed on the tenth day and in the

wheel-chair on the fourteenth day. This is governed largely by the condition of the patient. Several patients were confined advisedly to bedside care four to six months after operation in order to ensure a cure.

ANALYSIS OF CASES

Of the 50 cases, thirty-one were women and nineteen were men. The age limit was from sixteen to sixty-five. All of the 50 cases except one were of the cavernous type of tuberculosis. Three of these cases had, in addition, tuberculous empyema, following pneumothorax treatment.

Twenty-four cases at one time or another had been given pneumothorax. In most of these cases the result with pneumothorax was only partially satisfactory. (In one instance, the patient had carried a pneumothorax for six years and desired a permanent collapse because of the inconvenience of remaining near a hospital for refills. Treatment was necessary because of a stiff, atelectatic lung associated with an artificial dextrocardia). In seven of these cases thoracoplasty was intended as the ultimate form of treatment, but, due to the activity of the disease on admission, it was felt that a temporary collapse with air was the safest course to follow.

Valuable information was obtained by the introduction of air, as to the presence or absence of adhesions and the flexibility of the mediastinum. In 5 cases gomenol in 10-cc. amounts was introduced into the pneumothorax cavity in the hope that fluid would form and that the resulting adhesions would fix the mediastinum. The results were not conclusive, however, for, although fluid formed, fixation did not seem to be more complete than in those cases in which this procedure was not employed. Lungs which were the most difficult to collapse were not necessarily those with extensive infiltration but rather those with a moderate amount of infiltration. A cavity, situated anteriorly and proximate to the hilum with considerable good lung tissue surrounding it, was difficult to collapse.

Ten of the 50 cases had had phrenic-nerve operations, either avulsion or the removal of a few centimetres of the nerve. None of these were done preliminary to thoracoplasty, but were incidental cases, all of which had been done at least six months previous to the thoracoplasty. The results in these cases are not noticeably better than in those without paralysis of the diaphragm. Five of these 10 cases had, in addition, artificial pneumothorax.

Three cases were complicated with tuberculous empyema. Two cases required three operations, the first two posteriorly and the third through a U-shaped incision which permitted the extensive removal of the anterolateral portions of the 4th to 10th ribs inclusively. Despite the chronicity of the empyema cavities and the great thickening of the pleura, complete closure was effected. Aspiration of pus was, of course, necessary for several months, but obliteration of the cavity was fairly rapid once the chest was immobilized. In the third case mentioned, a good collapse was secured by the removal of sections of 10 ribs, in two stages, through posterior incisions.

The number of sections of ribs removed from any patient was from 3 to 11. Three sections of ribs were removed in 4 cases; 4 in 3 cases; 5 in 11 cases; 6 in 6 cases; 7 in 2 cases; 8 in 5 cases; 9 in 1 case; 10 in 14 cases; 11 in 3 cases. A bilateral thoracoplasty was performed on one patient, and four sections of ribs were removed from one side and three sections from the other side. In 15 cases it was deemed expedient to remove ribs through an anterior or anterolateral incision. Except in 3 cases of basilar cavities, the upper stage was done first.

COMPLICATIONS

Three cases in this series developed a pneumonic consolidation of the lower lobe due to bronchiogenic spread, following an upper-stage operation. These, of course, required further surgery. One case developed an effusion which later became purulent and was successfully drained. This same patient developed a marked shift of the lower mediastinum, resulting in extreme dyspnoea and tachycardia from which the patient recovered.

In 10 cases healing of the wound was retarded because of aseptic necrosis of the skin on the axillary side. Deep sloughs 4 to 5 cm. in diameter occurred in two of these cases.

One patient, two days following operation became ill with a violent diarrhoea which proved to be amoebic dysentery.

Nearly every case showed some slight injury to the brachial plexus, manifested by hyperaesthesia or paraesthesia, usually along the medial surface of the arm, forearm and hand. These symptoms were not troublesome and always disappeared usually within the course of a week. In addition, there was of course a partial anaesthesia over the scapula due to section of the cutaneous nerves.

DISCUSSION

In this series of cases the absence of fatalities is due in part to the small number. The cases selected were relatively good risks, not only from the standpoint of tuberculosis, but also from the standpoint of general health. Thirty-six had some degree of disease in the contralateral lung, but no case, except one, was operated upon until the disease was considered inactive. This case had a small cavity in each apex and a bilateral operation was performed.

All of our cases were definitely improved. There was a marked reduction in sputum. Forty of the 50 patients had no sputum, or had negative sputum after several months. There was a marked, gradual gain in weight. The bronchial stump on the operated side, however, may discharge pus, although negative for tubercle bacilli, several months after operation. This site is susceptible to acute respiratory infections.

Thoracoplasty in this series has permitted a return to normal life of many hopeless cases. This saved the patient and the institution in which they resided both time and money. Patients who were admitted to this institution and who were in a condition to be operated upon shortly after admission, remained in the hospital an average of 111 days, while those who were trying to effect a cure before accepting thoracoplasty stayed, on the average, 674 days. The length of a patient's life prolonged by thoracoplasty depends of course on a proper rehabilitation in a favorable environment. Time is needed to prove more conclusively the positive results obtained by thoracoplasty, but the results in this series can be optimistically contrasted with the results of Wiener and Fishberg (1), who claim that 80 per cent of their 44 patients operated upon derived no benefit from thoracoplasty.

SUMMARY

1. A report of 92 thoracoplasties on 50 consecutive cases of pulmonary tuberculosis is presented. Thirty-one had partial, eighteen had total, and one had a bilateral thoracoplasty. There was no operative mortality.

2. An anterior thoracoplasty is advocated prior to a posterior operation in those cases in which the entire rib is to be excised to effect a collapse.

3. Nitrous-oxide-oxygen with no synergist approximates the ideal anaesthesia for thoracoplasty.

4. These statistics bear out the fact that thoracoplasty should not be offered to a patient as a last procedure to cure a wasting systemic disease.

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THE FIRST CASES OF PULMONARY TUBERCULOSIS TREATED BY ARTIFICIAL PNEUMOTHORAX IN CONNECTICUT

HENRY F. STOLL[1]

As artificial pneumothorax is so widely used in the treatment of tuberculosis and recently has been successfully employed in lobar pneumonia, it may be of some historical interest to report the first two cases that were given this treatment in Connecticut over twenty-five years ago.

Dr. Samuel Robinson of Boston was the first to use pneumothorax treatment in the eastern part of the United States; and he injected his first case, a patient of Dr. Joseph H. Pratt's, a few months before the cases herein reported.

Cases

1: M. M., aged 28, married, consulted me in the fall of 1909. She had had a "stomach cough" for several years and "nervous prostration" when in High School. Tuberculosis was finally diagnosed and the two preceding years had been spent in Denver and Saranac Lake. Early in 1910, the late Dr. O. C. Smith of Hartford returned from a visit to Chicago, where Dr. John B. Murphy had told him of his results in treating tuberculosis by pneumothorax. As Mrs. M. M. had a daily temperature of a degree or two and a cavity in the lower part of the left lung posteriorly, we decided she was a favorable case for the new treatment.

Nitrogen was recommended for the compression but, as none was available commercially, Professor Riggs of Trinity College, kindly supplied me with it for several months. It was collected in a glass jar, under water, transferred to the rubber bladder of a football and transported by horse and buggy to the patient's home, great care being taken to avoid a puncture. An ordinary laboratory standard with rings, was employed to hold the two bottles. An Emmett trocar was introduced into the chest and one "listened" for the sound of the moving lung. The gas was then injected without manometer control. The first treatment was given February 2, 1910. After an unsuccessful attempt to estimate the pressure by mercury manometer, between four and five hundred cubic centimetres of nitrogen were injected. My notes were as follows: "The patient first complained of slight pressure but this did not last.

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Following the injection, there was a tympanic note over the lower lobe with distant amphoric breathing. The coin sound was not heard. Heart apex did not appear to change its position." The treatment was given at the patient's home and, at its conclusion, she went into the dining-room for her dinner. The following day the sputum was slightly blood-streaked: a week later a note stated that "the temperature, previously 100–101, had been below 100 and the pulse was somewhat slower." An X-ray was taken but was not very satisfactory: the size of the cavity did not appear to have been influenced. Twelve days following the treatment, the signs of pneumothorax had entirely subsided. At this time the patient's cough was less and the sputum was less purulent. Seventeen days after the first treatment, 633 cc. of nitrogen were injected. The sputum was again slightly blood-streaked the next day and, owing to the large amount of gas injected and the large size of the chest puncture necessitated by using an Emmett trocar, she developed subcutaneous emphysema from the clavicle to the crest of the ilium. She was rather uncomfortable for a few days and had a slight elevation of temperature but this did not persist. She shortly left for Asheville, North Carolina. The treatments were not continued, as this form of therapy had not as yet been used there.

The injury she sustained to the lung resulted in a slight pulmonary fistula which for a time necessitated her wearing a small piece of gauze: more annoying, however, was the fact that, when she would cough unexpectedly, the sudden expulsion of air from the fistula so closely resembled the passing of flatus as to be a source of embarrassment at times.

2: E. P., an unmarried woman aged 27. It was evident from her history that she had had tuberculosis for eighteen months before it was recognized. She had taken the cure for a long time at Saranac Lake and returned home as she was steadily failing. There was a daily temperature of 102°–3°, and extensive ulcerative tuberculosis of the whole of the right lung with multiple cavities. The left lung was infiltrated from the apex to the third rib. On March 3, 1910, with the assistance of Dr. F. B. Willard, 550 cc. of nitrogen were injected. The patient did not experience any distress other than a slight feeling of constriction. Toward the conclusion of the treatment, slight pleurisy pains were felt. No cough was present either during or following the treatment. Following the injection, the percussion note was markedly tympanic over the lower half of the chest. Voice and breathing were distantly amphoric up to the angle of the scapula and, above this area, sounds were distant, with small moist râles. No blood-streaked sputum followed the treatment, and the lung appeared to be well collapsed from the third rib downward in front and posteriorly from the angle of the scapula.

When the patient lay on the compressed side she experienced a sensation

of "pulling" within the chest. A note fifteen days later reads: "The breath sounds and râles are heard one space lower than the week before. The patient raises less though still has a hard cough, feels better, has a better appetite and temperature is below 100."

Twenty-five days later the gas had all been absorbed. The signs of cavity were again very evident but there were much fewer râles than before the treatment, and 390 cc. of nitrogen were injected. This was followed by slight subcutaneous emphysema. The patient's cough was much less and her temperature became lower. On April 5th, one month after the treatment started, she "felt much improved, toxic symptoms were practically all gone, cough and expectoration were much less, temperature normal for five days—for the first time in several months." About three weeks later, the patient developed pain in the base of the other lung. Pleurisy was suspected.

When the signs of pneumothorax had entirely subsided, the temperature began to rise again and, May 11th, 520 cc. were injected; however, as the trouble in the left lung increased it was not thought advisable to continue the treatments. The injections, however, quite definitely seemed to slow up the course of her disease. She later showed signs of intestinal involvement. One further treatment was given, to satisfy the patient and her family, of 550 cc., which was again followed by subcutaneous emphysema.

Several other cases were treated during the succeeding years, but, as all were far advanced and as the need of frequent injections was not appreciated, no startling results were obtained though lives were undoubtedly prolonged.

It was interesting to observe that, when the lung expanded after compression, the râles were much less and it seems strange that it did not occur to us to try to maintain collapse by frequent compressions.

The question as to why Dr. Murphy gave up the treatment has been frequently discussed. My recollection is that he said he did so because he felt its continuance would force him out of general surgery which interested him more.

PLEURAL SHOCK[1]

CHAS. HARTWELL COCKE[2]

It is somewhat surprising that the subject of pleural shock or air embolism has never been discussed save in passing mention by this Association. Perhaps no other nonspecific form of therapy in any disease has had more enthusiastic acclaim and usage within recent years than has compression therapy in tuberculosis. It seems superfluous to add that of course artificial pneumothorax is by far the commonest form of compression used. I have no possible means of estimating the number of times the pleura is punctured daily in this country in the course of such treatments. Add to this number the large number of other occasions demanding pleural entrance, such as for removal of fluid by needle or drainage, for lavage, etc., and the total must mount to high figures. This is particularly true of late, with the very widespread use of pneumothorax and with the further expansion of its indications and usages by reason of accumulating knowledge and experience.

And every so often something quite dramatic happens that leaves an indelible impress upon the physician's memory,—fortunately very little upon the fate of the patient, save in that unfortunate 10 per cent or less of cases that immediately result fatally. I refer, of course, to what Roger as early as 1864 called "pleural eclamptic fit," later known as pleural shock, pleural reflex syncope, air embolism, etc. Why such a dramatically terrifying, although admittedly and fortunately rare, an experience as pleural shock should not have been considered of sufficient moment to warrant discussion by this body, when only a few years ago we waxed eloquent as well as warm on all the various phases of pneumothorax work, is perhaps not important. Perhaps its fortunate rarity is ample reason for this neglect; perhaps its difficulty of explanation has been somewhat forbidding. To me, this very difficulty is one of its most intriguing features. I seek,—I do not propose the correct answer.

Without perhaps statistical warrant, it has seemed to me that most

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[2] Asheville, North Carolina.

recent writers, in mentioning the subject, assume that all so called pleural shock is the result of an air embolism. It is just because I dissent from this view that I make this short communication.

In the brief compass of time allotted, it is not worth while to review the experimental work which has been done on the subject, save to say that irritating substances injected into the pleura of healthy animals may produce epileptiform crises, with modifications of blood-pressure, while it is a very difficult thing to produce a gas embolus in a healthy animal. In another place (1) I have briefly discussed some of the experimental work and its confusing and altogether unsatisfactory results. The prime reason for this is doubtless the at present insuperable difficulty of reproducing the phenomenon in the animal.

In brief, the characteristic features of pleural shock are a sense of discomfort, pain or constriction in the throat, cardiorespiratory embarassment (sometimes pulmonary oedema), tonic and clonic contractions of the muscles, loss of consciousness, and in some instances sudden death. The occurrence of such a syndrome has been noted under such diverse conditions as (a) pulmonary operations; (b) exploratory and aspiratory punctures; (c) pleural lavage and dressings; (d) at the beginning of (before the entrance of air), and during and after punctures for pneumothorax. Chabaud (2), in his review of the subject of the nervous accidents occurring in the pleuropulmonary interventions written in 1926, cites *seven* instances occurring spontaneously in the course of pleuropulmonary disease, provoked by no intervention. I have seen no immediately fatal cases, nor have I seen paralysis, monoplegic or hemiplegic, mentioned by many writers. In these latter, the assumption of embolic origin would seem plausible.

What of its frequency? I have been engaged in pneumothorax work for twenty years. My associate, Dr. Crow, and I have entered the pleura between 7,000 and 8,000 times. I have seen two minor, one moderate, and one major instance. Descriptions of three of these instances have been published (1) elsewhere, and need no detailed repetition.

Briefly, one young man (M. D.), of 27, who had been undergoing pneumothorax for eighteen months, with excellent collapse and no adhesions, during the course of treatment, while otherwise feeling apparently well suddenly began to complain of queer feelings, a sense of constriction and suffocation in the throat, an acute pain radiating to the left kidney and down the left arm (it was a left-sided pneumothorax), and went into mild syncope. Discontinuance of the

treatment was followed by a rapid recovery from the syncope and pain. Four days later I gave the patient a refill without incident; he continued his pneumothorax another uneventful year, passing through a dramatic episode of malignant neutropoenia, also reported elsewhere (3), recovered, and has been at home in Indiana, well for nearly two years.

The most dramatic case I have seen was that of a young woman of 22 (C. T.). At a third attempt at pneumothorax, just as the novocain needle (18-gauge) was in the region of the pleura, the patient said she felt queer. Wondering if I were really in the pleural space, I connected the hypodermic needle with the manometer, but there was not the flicker of a motion in the manometer (water). Immediately the patient went into syncope, was blue-gray in color, and had no palpable pulse anywhere; her pupils were widely dilated, and her heart action too feeble to be discerned by the stethoscope. Pulmonary oedema rapidly ensued, with bloody, frothy sputum. Adrenalin chloride was injected deep into the precordial region with return to consciousness in half an hour, and prompt relief of the pulmonary oedema. Definite bradycardia was present and persisted for twenty-four hours. After this there was a definite increase in pulmonary tuberculous activity, with death twenty-one months later from progressive tuberculosis and repeated haemorrhages.

In October, 1932, after three or four unsuccessful attempts at entry, my associate, Dr. Crow, found an apparently free negative space, injecting 400 cc. of air in a young woman of 36 (L. S.). This produced a positive reading, which, however, promptly returned to negative. Three days later, with needle in the same area, the manometer showed -4, -0. One hundred cubic centimetres of air was slowly injected, with no change in the manometer, and 300 cc. more air was put in. The last reading was 0, $+4$, which again promptly returned to a negative. I had left the room a moment or two when I was called back. The patient complained of a choking sensation around the throat and became unconscious, with convulsive seizure of the voluntary muscles of the face, neck, arms, chest, and legs (lasting only momentarily, however). The pulse was imperceptible, but the heart-sounds, heard with the stethoscope, were found to be quite slow and regular. Bradycardia persisted some hours. Adrenalin-chloride injections, heat and ammonia inhalation resulted in a prompt return to normal in every way in fifteen minutes. There were no sequelae and no apparent influence on the tuberculosis. Was this pleural shock due to pressure of the air on a sensitized and fairly well-bound pleura, with the possibility of the pressure coming from air intrapulmonarily introduced? Certainly no evidence of paralysis or eye disturbance was discovered, though carefully looked for.

I recite briefly from a recent report (4) three fatal cases.

Bedridden, febrile patient had been taking pneumothorax for several months. Puncture in usual place. Before injection of air, patient uttered a cry, complained of retrosternal anguish, remained unconscious; no hemiplegia; but died in five minutes. Again, a man of 37, whose first three injections were done without incident (there being a free pleural space), at the fourth injection, with free oscillation of the manometer, 200 cc. of air was introduced. At this moment, the patient suddenly raised up, complained of pain at the point of entrance. Hemiplegia; rapid cyanosis; thready pulse; patient dead in two hours. Lastly, patient of 32 years, after the fifth injection, gets up and dresses. She goes into the next room, puts on her coat, cries out, and falls down with severe dyspnoea. Death in a few seconds.

Can these happenings all be explained on a single basis? Is there a single mechanism at work? Frankly, I feel that the burden of proof is upon those who would attribute all these accidents to air embolism.

Consider the number of times the pleura is punctured daily. Constantly not only inflamed pleura but lung must be punctured. If it is such an easy explanation as the proponents of air embolism would have us assume, it is quite astonishing that it is not of fairly frequent occurrence rather than an exceptional experience. I am sure that any person doing pneumothorax work in any amount has not occasionally but several times injected air directly into pulmonary tissue without any suggestion of embolism. I recall quite definitely one instance of a patient who was supposed to have been taking pneumothorax from another physician regularly every ten days for eight months, who presented when I first saw her not the slightest evidence, by examination, fluoroscopy or film, that there was any air in the pleura, in spite of the fact that regularly she had received at ten-day intervals about 500 cc. of air, doubtless intrapulmonarily. Repeated punctures on my part failed to reveal any free pleural space. Frommel and Demole (4) cite a case similar to the one I mention in which 25,000 cc. of air had been put into the lung (50 injections of 500 cc. each) without the least accident. I could cite numerous similar instances. In no case of known intrapulmonary injection of air have I seen pleural shock, unless the case of L. S., recited earlier in this communication, has such an explanation; but if this were the case here, I incline to the explanation of intrapulmonary pressure or pull on an inflamed pleura as the cause of the syndrome, rather than an air embolism. Frommel and Demole (4) state that, in a review of 250,000 injections reported by French colleagues, the intraparenchymatous insufflation of air was not accompanied by any grave symptom. It would seem reasonable, therefore, to assume that certain pathological conditions must be met in order that air embolism produce the condition under discussion.

Many observers have proved the innocuousness of injecting air into the pulmonic parenchyma of the healthy animal.

Incidence: Fortunately, the graver manifestations of the condition are rarely met with,—on an average about two or three times per 10,000 injections. Undoubtedly it happens much more frequently at the first effort at pneumothorax than at later trials, one reason naturally being that there are so many more refills than original entries. Sex and age seem to play no important part so far as my observation goes, in spite of the claim of some writers who try to implicate the more highly nervous make-up of women as a predisposing cause. The condition may occur before, during, and at the conclusion of the injection. Also pleural shock has been frequently reported during pleural lavage with various forms of irrigating liquids, during pulmonary operations such as drainage of an abcess as well as during exploratory and aspiratory needling.

Its effects: In the review of 300,000 (corrected) or 250,000 (uncorrected) injections made by Frommel and Demole (4), there were reported 63 immediate accidents, of which fifty-eight were transitory and only five fatal. The mortality of the accident in this series was thus less than 10 per cent. Less than a third of the accidents failed to be accompanied by symptoms of nervous localization, while more than two-thirds manifested such disturbances as paralysis, monoplegias, hemiplegias, aphasias, with or without epileptiform crises or blindness. When symptoms of localization did occur, many lasted only a few minutes, a certain number a few hours, and a hemiplegia for a month; but all recovered. One case of amaurosis persisted fifteen months, till the patient died of generalized tuberculosis. So much for these statistics. The authors admit the unsatisfactory nature of their origin from diverse sources, perhaps not always meeting the rigorous exactitude of scientific guarantee, but they serve for this discussion. In my own short series (and may it never be much greater in numbers!), I have failed to observe any paralytic effects; and, save in the case in which pulmonary oedema ensued, no really serious results. All the other cases, save the last (L. S.), continued their pneumothorax without recurrence of the accident. In this last case the effort was discontinued, as it was felt that pleural symphysis was definitely proven.

Pathology: Too little of authentic value is really known about the fatal cases to justify extensive discussion. The difficulty of discovery of the embolism in even the fatal cases is admitted.

Its cause: The phenomena have only two rational explanations (and perhaps only one)—air embolism or true pleural-reflex syncope. If air embolism is the only cause, I fail to understand its mechanism in pleural lavage and in the changing of a drain. It would also seem remarkable that the hundreds of instances in which air has been injected intrapulmonarily have not produced the condition with the almost certain opportunity for the air to reach the pulmonary vascular system, both arterial and venous. (The innocuousness of slight air-bubbles in the venous stream would seem probable from the vast amount of venous medication and injections currently practised without adverse report.)

If there is such a condition as pleural-reflex syncope (pleural shock), it is well to review briefly the nerve-supply of the pleura, and also the evidence of its capacity to initiate reflex activities, if an approach to understanding is made. The innervation of the pleura is as follows; the *parietal* from the intercostal, sympathetic, and vagus nerves; the *visceral* by fibres from the pulmonary plexuses originating in the vagus and sympathetic nerves; while the *pericardial* pleura receives two delicate branches of the vagus coming from the *plexus pulmonalis* or *plexus oesophageus*, most authors believing that the phrenic also supplies some fibres to the pericardium. The *diaphragmatic* pleura probably has both motor and sensory fibres from the phrenic, while Cavalie (5) has shown that the last 6 intercostal nerves penetrate 1 to 2 cm. into the margin of the diaphragm and supply the muscle, and probably supply some sensory fibres to its overlying pleura. It is generally accepted that the alveoli of the lung have no sensory innervation. They have exactly the same nerve-supply as the visceral pleura; hence pain sensibility in the visceral pleura is viewed with scepticism. Capps (6) states that all the more recent anatomical and experimental studies confirm Luschka's theory that inflammation of the phrenic-nerve endings in the diaphragm are responsible for cervical pain. In his experiments upon the pain resulting from pressure upon the diaphragm, Capps found that, as his wire moved from the outer border toward the centre, the pain as a rule suddenly changed, and was referred to the neck. This occurred in 23 of 35 cases. Pain was sharp and lancinating, and referred to the certain areas overlying the trapezius-muscle ridge. He found also that the pain evoked from the parietal pleura has all the characteristics of peripheral nerve pain: namely, the pain is located directly over the site of the irritation; there is tenderness to deep pressure over the intercostal nerves; and the skin is generally not hypersensitive. In no instance was irrita-

tion of the parietal pleura accompanied by pain in the abdomen. The pain proceeding from the pleura of the diaphragm is entirely different. The lateral and anterior margins and posterior third of the diaphragm give rise to pain, not locally in the diaphragm, but in a different area of the lower thorax, back, and abdomen. A true "referred pain" is segmental in distribution, located in the peripheral tissues, more particularly the skin, and is accompanied by tenderness and often by muscular rigidity. Also the neck pain, originating from irritation of the inner surface of the diaphragm, is a typical "referred pain." There is every reason to suppose that the afferent impulses from the diaphragm are carried up the phrenic nerve to the cervical cord, with resulting painful stimuli, which are set up in the corresponding cutaneous segments. As the phrenic nerve is made up largely of fibres of the 3rd and 4th cervical nerves, the resulting referred pain from phrenic stimulation is readily found in the 3rd and 4th cutaneous segments.

Several years ago, in explanation of pleural shock, I utilized the hypothesis of Meakins that there is a reflex action between the pleura and the pulmonary circulation; that under given, uncommon conditions, this reflex is brought into play; and as a result there is a profound disturbance of the pulmonary circulation. As far as present knowledge goes, this disturbance is quite likely to be a spasm of the finer pulmonary circulation, leading to a very rapid rise in the pressure of the pulmonary circulation and a great decrease in the volume of blood reaching the left heart. This is consonant with the fact that in these cases of pleural shock there is observed a rapid decline in the volume of the peripheral pulse, and quite obviously cerebral anaemia, with syncope and unconsciousness. This would likewise account for the appearance of pulmonary oedema, when it occurs. There is also ground for the assumption that the reflex may extend to the systemic circulation.

What of analogous conditions?

Vaso-vagal attacks: Sir Thomas Lewis (7), in his recent small but most practical book on *Diseases of the Heart*, has this to say with regard to vaso-vagal attacks: that this is the commonest form of syncope, that it occurs in both sexes, more generally in the young, though not exclusively, and that chronic illness predisposes, while fatigue is a not uncommon attendant. The attack is a probable cause of fainting in response to certain forms of pain, such as in coronary thrombosis or renal colic. Nervous and emotional distress is commonly provocative. The provocation may be adequate without arousing marked feelings of fear or

dread; there is frequently an element of surprise, as when the patient sees the blood flow into a syringe (or even at the sight of a hypodermic injection, as I have seen). The attack usually occurs while the patient is standing or sitting, rarely if lying down. The central feature is, of course, syncope. There is a progressive fall in blood-pressure and pulse-rate, which may be imperceptible. There is pallor of the skin from simple drainage of the blood from the skin. Gradual loss of consciousness follows, with flaccidity, and some dilatation of the peripheral vessels, with lost conjunctival reflexes. Slight clonic movements of the face, upper limbs and trunk occur. Respirations are slow, deep, and sighing. Sweating is often free. The attack is quite brief,—two to ten minutes. Recovery is slower than the attack, leaving the patient weak and tremulous, and sometimes with a severe headache. The slow heart is due to increased vagal tone, and the low blood-pressure due to dilatation of the blood-vessels in the splanchnic area. It is the vasodilatation that is responsible for the loss of consciousness. Hence the term, *vaso*-vagal, aptly descriptive of the two effects, points out the dominant features of the attacks. It is believed that the attacks are caused by reflex *disturbance* of a central nervous mechanism, which is normally set in unexaggerated motion by stimulation of either the carotid sinus or the depressor nerve.

At the recent meeting in Atlantic City of the *Association of American Physicians*, Weiss demonstrated that not only the carotid-sinus reflex but also vago-vagal reflexes can induce sinoauricular rhythm, ventricular standstill, and also complete block. He called this reflex *vago-vagal reflex* because it starts at the sensory nerve-endings of the vagus, from which the impulses come up through sensory afferent nerves to the medulla vagal centres, from which motor impulses are discharged through motor vagus fibres, which vibrate to the heart. He found in the cases under study that the source of the afferent impulses is in the diverticulum of the œsophagus, or in the tonsils, or in the superior laryngeal nerve. He adds, "But if this is true, there is no reason why at times afferent impulses from the pleura cannot set up such reflexes."

The close analogy between vaso-vagal, vago-vagal attacks and pleural-reflex syncope is thus quite obvious. Just as Lewis states that the vaso-vagal attacks are believed to be caused by a reflex disturbance of a central nervous mechanism, which is normally set in motion by stimulation of either the carotid sinus or the depressor nerve, I presume to offer, as an explanation of pleural-reflex syncope, that it is a condition produced by

reflex activity from injury or insult to an inflamed pleura under unknown and uncommon states, similar in many respects to the vaso-vagal attacks of syncope.

That air embolism is a real occurrence I do not for a moment deny. That it further produces a syndrome quite similar to pleural shock is obvious. In some instances of death, it undoubtedly has been the cause of cerebral haemorrhage; but this is not always discovered at autopsy in all fatal cases. I repeat, however, that at present I believe that it is quite probable that shock from air embolism is probably a rather rare occurrence, whereas shock from pleural irritation is probably a relatively common occurrence.

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PULMONARY TUBERCULOSIS IN THE AMERICAN NEGRO[1]

Do Environment and the Attitude of the Patient Affect His Disease?

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We are beginning to obtain a much more definite idea as to the manner in which pulmonary tuberculosis occurs and progresses in the American Negro. This better understanding of this very puzzling subject has been obtained from the work of Opie (1), Pinner and Kasper (2), Bogen (3), Goldberg (4), Everett (6), and many others. Despite the fact that the death-rate of tuberculosis for the population at large has diminished markedly in the past decade, Pinner and Kasper (2) note the fact that the tuberculosis mortality in the Negro, as observed in Detroit, has risen rather than fallen during the same period, going from 303 in 1920 to 447 per 100,000 in 1928, while the respective figures for whites were 93.3 and 68.2. Statistics of the Metropolitan Life Insurance Company, compiled by Dublin, quoted by Opie (1), from 18,500,000 white people and 2,500,000 Negroes, show that the average death-rate per 100,000 from 1925 to 1927 was for the white race 69 and for the colored race 203, a ratio of approximately 1 to 3.

Pinner and Kasper (2) have put in a few short sentences the various explanations which have been advanced to account for the discrepancies occurring between tuberculous infection in the two races:

1: The Negro, having been in contact with tuberculosis for a much briefer time than the white, has not as yet had an opportunity to acquire the same measure of "inherited immunity."
2: The Negro escapes childhood infection more frequently than the whites; therefore an infection acquired later in life occurs in virgin (nonallergic) soil and produces rapidly progressive (more or less) "childhood type" tuberculosis.
3: The apparent differences are *toto coelo* due to environmental conditions and to the mental attitude of the Negro in regard to disease.
4: There exists a true racial (genotypic) difference between the two races (entirely mysterious in character), which confers high resistance on one and low resistance on the other race.

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When the preparation of this paper was first begun there were several facts which were very evident to us. The pulmonary tuberculosis that we see here is met as one of the problems of the day in a hospital devoted to the taking care of individuals suffering from all manner of diseases. We were more interested in the Negro than we were in the tuberculosis; and it has occurred to us that some contribution from this viewpoint might not be without its value and interest.

The series of cases, one hundred occurring in each sex, is, of course, entirely too small from which to draw any statistical knowledge; but the groups were selected because we believe they represent a much larger group typical of the community in which they live. This community might be described in some detail to understand the problems which we faced.

The Employees' Hospital, Fairfield, Alabama, with a normal capacity of 300 beds, is so divided that the census from day to day represents about 55 per cent colored and 45 per cent white. The material for this study was drawn entirely from our own employees; and the X-rays made in this series and the hospital records from which the information was compiled were all prepared here in our hospital. All X-ray plates referred to in this article, and such as are shown, were almost without exception made within twenty-four hours after admission of the patient to the hospital.

The Tennessee Coal, Iron and Railroad Company is engaged in the mining of ore and coal, and in the manufacture of steel products on the outskirts of the City of Birmingham. Our total employment list, averaging in good times about twenty-odd thousand men and their families, representing a total of seventy-odd thousand human beings, is composed of 60 per cent Negro and 40 per cent white. Our mining population is 90 per cent Negro and 10 per cent white.

In order to have a proper understanding of the manner in which these people are encountered, a word should be said about the development of the Medical Department of the Tennessee Coal, Iron and Railroad Company under Doctor Lloyd Noland for the past twenty years. A reorganization of the Department in 1913 placed all the employees who live in our mining districts under our medical care. Doctors were paid a fixed sum of money per month to take care of individuals and their families. Those under our medical care at and below a certain economic level are permitted to call a physician any time they desire without any additional expense. The hospital is so arranged that patients on this

list are allowed ward rates far below actual cost, so that admission to the hospital entails very little additional outlay.

These matters are mentioned because they bear a definite relation to the subject under discussion, when later on we take up the importance or lack of importance which environment plays in the development of this disease in the Negro race.

Beginning with 1913 tremendous improvements were made in the housing of our employees. Since that time numbers of what might be termed "model villages" have been constructed, and many repairs and changes have been made in the older villages, so that in the ore and coal mines, which hire a large proportion of our Negro employees, living conditions compare very favorably with those of the general population in a vicinity of this character. They live in well-kept houses, with excellent water-supply and sewage disposal. The houses are surrounded by grounds in which gardens can be grown; and the opportunities for exercise and recreation are ample. Viewed by the ordinary standards by which we judge such things, the living conditions, as far as health, sunlight, exercise, and opportunities for recreation, etc., are concerned, compare very favorably with those of even well-to-do people living in cities. Not only are the housing conditions almost ideal, but in good times the rate of pay to the wage-earner of the family is ample to supply—and does supply as far as we can find out—plenty of food of a nourishing and very excellent character. In each mining community commissaries are located where nothing but food of the highest class is kept, and a pasteurized milk-supply is on hand in the commissaries at all times. Fresh meats and vegetables are provided at a cost considerably below that which the average individual pays in a city.

Analysis of these 200 cases of pulmonary tuberculosis showed some minor differences in the two sexes. The average age of the males was, in round numbers, 32 years on admission, and that of the females was 26 years.

I think these 200 cases represent a fairly accurate pattern of tuberculosis, as seen in this hospital among our Negro patients and in this Negro community as a whole. It will be noted in the record of occurrences by decades that many more females entered the hospital in the second decade of life than males, the relative figures being 25 females and 7 males. The decline in incidence after the third decade is more abrupt in the females than in the males, which is in accordance with the findings of other observers.

The X-ray findings were interesting and showed almost 100 per cent of advanced tuberculosis occurring in females, with similar high figures among the males.

With the exception of the few age differences in the two sexes, the X-ray and clinical findings in this group resemble very closely many other larger groups which have been collected in reference to pulmonary tuberculosis in the Negro. We think the resemblance is very striking indeed.

From the analysis of this short series of cases a number of facts are plainly evident. Regardless of the extent to which tuberculosis occurs, the living conditions, food supply and character of surroundings, in their relation to light, fresh air, and exercise, seem to have affected the progress of the disease, once it has become established, little, if at all. Despite the fact that a competent medical service is at their disposal without any extra cost for the treatment of tuberculous cases, the individuals present themselves to our physicians for the first time suffering from an advanced type of the disease, just as does the impoverished Negro in the slums of a northern city. This is all the more surprising in that almost all of our physicians are southern-born and bred, with as accurate a knowledge of the supposed Negro psychology as the white man ever comes to possess. Most of them have had charge of our various camps for years and know the inhabitants intimately. They present to a rather remarkable degree many of the aspects of the much-regretted old-time family physician, and yet they see their charges for the first time when the latter literally have one foot in the grave.

The "why" which we have so often asked ourselves still remains unanswered, but we have evolved some theories in regard to the matter. They have followed the line of greater interest in the patient than in the disease.

We have evolved three ideas as to why our patients are seen so often for the first time with a death from tuberculosis at their very elbows. It is true that these theories are refuges after analysis of environment, food-supply, and the question of expense have failed us.

1: Tuberculosis is a painless disease.
2: The Negro may suffer from an advanced tuberculosis of the lungs without ever becoming aware of it.
3: The Negro is aware of his condition (pulmonary tuberculosis) and endeavors to conceal it.

We are thoroughly aware that none of these ideas completely explains

all that we see, but we believe that one or more of them enters into the problem of each individual case. These theories are incapable of proof and have been arrived at by studying the stories and personalities of our patients. Permit us to present several short case histories in support of them.

Two years ago a Negro, thirty years of age, was brought into the hospital in a state of collapse. He was bleeding from the nose and was coughing up quantities of bright red blood. When he had regained consciousness he told us he had had a slight cold for the past week, but had been at work every day, and that, outside of a moderate pain in the right chest at the time he was being questioned, he felt fully capable of returning to work. He had lost no time from his work in the immediate past. An hour before his admission to the hospital he lifted a five-gallon oil can to place it on an elevated stand. Immediately he was taken with a terrible pain in his side. The blood began to come from his throat, and he lost consciousness. An X-ray plate of his chest made immediately after his admission to the hospital showed a bilateral tuberculosis, tremendous in extent, and a spontaneous pneumothorax of the lower right chest.

It is hard to conceive of one of our race continuing on at hard manual labor with a fraction of this man's involvement. He died in the hospital two weeks after admission.

An elderly Negress of uncertain age, but believed to be in the sixth decade of life, was admitted to the hospital in December, 1932. She stated that up to a few months before she had been in perfect health, when she developed a cold and productive cough. She thought she had influenza; paid no attention to her symptoms; and continued at her household duties up to the very moment of her admission to the hospital. During her stay of five days she ran a "sky-rocket" temperature, although she insisted that there was little wrong with her. An X-ray picture revealed a pair of lungs riddled with cavities.

Why did these two patients come to us at all? The man came, of course, because he was picked up at the plant, placed in an ambulance, and carried to us. If he had not had the collapse of his right lung, no doubt he would have continued at work. We gathered from the surrounding circumstances that the old woman responded to some urging from without. We feel sure she would never have come of her own will. Whether or not she had guessed what ailed her, we never knew, but we presumed that someone had.

All that we can gather from the following case reports is that those who know most about our work have the least confidence in our powers to heal pulmonary tuberculosis. One of our ward maids was observed by someone in authority to be looking ill and to be nauseated. She was admitted. According to her story she had been sick at her stomach for several days past. Only on close questioning did she admit that she had had some fever and cough,—productive of saliva, she said, and that for only three days before admission. She had had no haemoptysis, but admitted that her nose had bled. Her temperature on admission was 104°, and both physical examination and X-ray plate concurred in their findings of an advanced pulmonary tuberculosis, with cavity-formation.

Another of our ward maids was seen to be not herself, and was sent to the Section. She was more frank. She had had fever and cough for several weeks, but not of such a degree as to force her giving up her work, which she had continued up to the time of her admission. Haemoptysis was denied. Her temperature was found to be 104°. The findings were those of an advanced pulmonary tuberculosis, with cavitation in the right upper.

The wife of one of our hospital employees, a bright young mulatto girl, while at home on the night of October 9, 1932, began to expectorate quantities of blood. At the insistence of her husband she came to the Admitting Department. Her husband was left outside the examining room, and in her interview with the Admitting Officer she omitted to mention the cause of her appearance at ten o'clock at night. Somewhat at a loss to explain her presence at that hour, he referred her to the Out-Patient Clinic, with no certain date. She returned to her home. Later that night the haemorrhage recurred, and again at her husband's demand she appeared at the Out-Patient Clinic in the morning. This time she acknowledged haemoptysis, but described it as very small in amount. The physician who examined her asked her to cough while he listened to her chest. The first effort brought forth a great gush of blood. We learned the true story later.

Here we have three young Negresses all above average intelligence,—two of them employees of our own hospital and one the wife of an employee,—all thoroughly conversant with hospital procedure and gossip; and all made light of their complaints and entered the hospital under duress. It would be unwise to presume that they did not understand with a fair degree of accuracy just what was going on inside their bodies. Two of them, it is quite certain, did their best to conceal the fact that

they had expectorated blood. Why? We think they must feel that when they give up that the end is not far off; that the spitting of blood is a deadly omen; and, so far as our treatment is concerned, they have no confidence in it. We have been noticing for a long time past that our Negro patients have the normal amount of curiosity as to what is the matter with them, and as to what their chances of recovery are. Once they have found out that they or their relatives have pulmonary tuberculosis, they ask questions no more. They conclude, we are sure, that all need for asking has departed. They no longer ask us but they ask themselves, and are guided to their answers by their own powers of observation and past experiences.

If we conceive of a true genotypic variety of tuberculosis to explain away the very puzzling condition in which we find so many of our Negro patients, the question of unconsciousness and also of fear must be given due consideration. We all know full well the fallacies of generalization. It is as idle to say that all Negroes live in fear, as it would be to say that all white men are palladins; but in regard to tuberculosis this is largely true. Their attitude might be defined as a mixture of terror and resignation.

Near us in Birmingham is a sanatorium for the treatment of tuberculosis, with a limited amount of accommodation for Negroes. It is conducted by a competent and able man. More than once our patients have declined our offer to secure a bed for them there. Their answer has been that members of their race never come out of there alive. It would be useless to point out to them that those who stay at home live but a short time. They are well aware of that. We must interpret their decision as meaning that they wish to spend whatever time is left to them with their own people and in pursuit of their own desires,—not a surprising decision after all.

We have been uncertain as to what it is that finally leads a Negro sick from pulmonary tuberculosis into our hands, but we have come to believe that the occurrence of haemoptysis is "the straw that breaks the camel's back." We judge this from the not infrequent efforts to conceal its happening. We have seen no evidence that the associates particularly fear the presence in their midst of an active tuberculous patient. They are certainly never denounced to the authorities. The Negro is too unthinking, too heedless, or most likely too kindly for this. He is so secretive in his relations with the white man and so clannish, that we doubt if any educational campaign could persuade him to the wholesale

disclosure of this disease in his own race. He endures his tuberculous infection in silence until a haemorrhage or a collapse forces him to the doctor to receive a melancholy *imprimatur* relating to facts on which he is already thoroughly informed.

SUMMARY

Two hundred cases of pulmonary tuberculosis equally divided between the two sexes and occurring in members of the Negro race are reported.

These patients are all either employees or members of families of employess of the Tennessee Coal, Iron and Railroad Company located in Birmingham.

These patients live under conditions almost ideal, as regards housing, food-supply, sewage disposal and water-supply, and have ample leisure and opportunity for healthful recreation.

They are in daily contact with competent medical service, and have shown every disposition to call for the services of our physicians in other diseases, with the exception of pulmonary tuberculosis.

When they first call upon a physician for treatment of this disease they are in the same condition as Negroes living in the slums of our northern cities.

Some explanation is sought for this unusual condition. It is suggested that the explanation lies in the psychic and autonomic responses of the Negro to this disease.

The following points are emphasized in order to explain in part the solution of the riddle:

1. Tuberculosis as a rule does not produce pain in the infected individual. It is pain that frequently decides the Negro to call upon a doctor.

2. The Negro can develop to a tremendous extent infection from tubercle bacilli without becoming aware of the fact.

3. It is the fear of being found out and the objection to being put under restraint which induce the Negro suffering from pulmonary tuberculosis to put off as long as possible the disclosure of his condition.

Analysis of 200 cases of pulmonary tuberculosis occurring in the American Negro

	Average age on admission
Colored males	31.9
Colored females	26.0

	Decade ages					
	Second	*Third*	*Fourth*	*Fifth*	*Sixth*	*Seventh*
Colored males	7	40	33	14	4	2
Colored females	25	49	19	6	–	1

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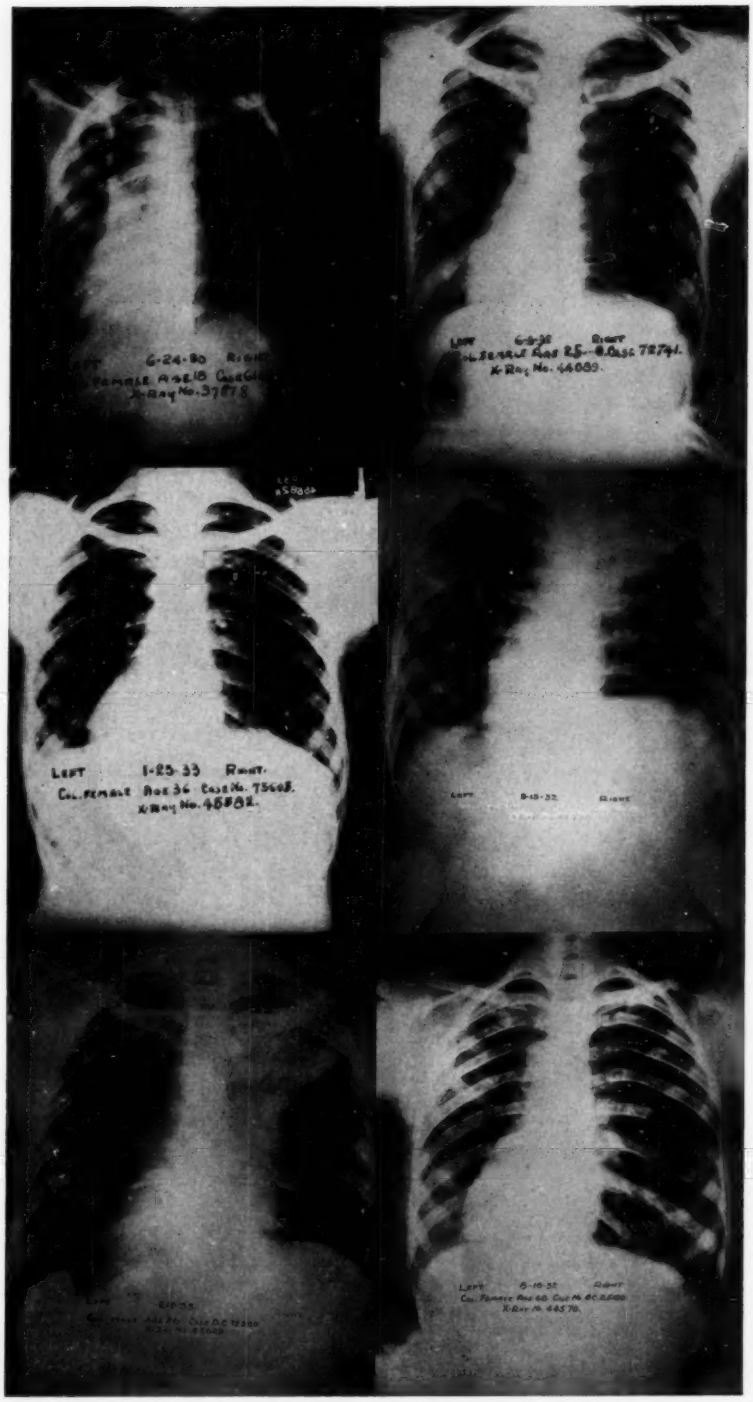

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIG. 1. Case 61,036. Negress. Age 18 years. First seen and admitted to hospital June 10, 1930. This picture was made June 24, 1930, after removal of 300 cc. of fluid from the left chest. Marked anaemia present. R. B. C. (three counts), 3,000,000; 2,600,000; 2,100,000.

FIG. 2. Case 72,741. Negress. Age 25. Admitted to hospital June 3, 1932. First seen and pictured on this date. Positive sputum obtained forty-eight hours after admission. Patient died at a tuberculosis sanatorium, October 2, 1932.

FIG. 3. Case 75,605. Negress. Age 36 years. Condition in chest discovered by accident. No previous history of pulmonary tuberculosis made out at any time. Both lungs showed many bilateral calcifications scattered throughout on both sides. Case resembles one of healed tuberculosis, with many focal points in both lungs, and is interesting on account of completely negative history. Patient was a rather intelligent Negress. Patient symptom-free at time picture was made.

FIG. 4. Case 25,437 (O. C.). Negress. Age 24 years. First seen and pictured September 12, 1932. Complaints were cough, expectoration, and loss of weight from 125 to 95 pounds in six months. Cavity-formation. Positive sputum. Bilateral involvement much more marked in the right upper. Pictures made the day after patient first consulted a physician.

FIG. 5. Case 12,200 (O. C.). Negro. Age 26 years. Picture made the day patient first consulted physician. Advanced pulmonary tuberculosis, right upper. Earlier type left apex. No history of haemoptysis. No cough at night. No pain in chest. Normal weight 170 pounds; present weight 165 pounds. Sole complaint, day-time cough. Temperature 99.4°.

FIG. 6. Case 25,120 (O. C.). Negress. Age 48 years. Patient pictured the day after seen by a physician. History of expectorating blood for two weeks. X-ray plate showed typical advanced active pulmonary tuberculosis, with cavity-formation. Pathological involvement is more particularly centered in the left upper.

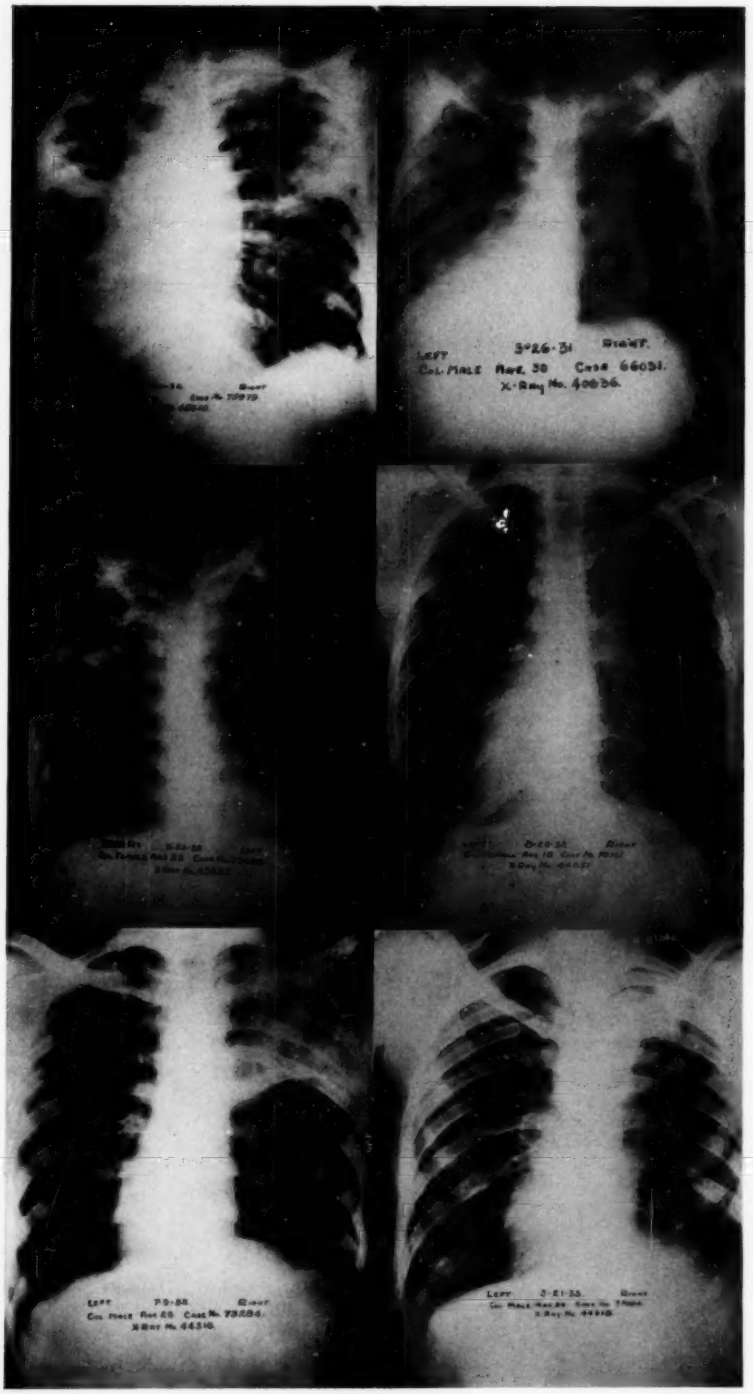

FIG. 7

FIG. 8

FIG. 9

FIG. 10

FIG. 11

FIG. 12

FIG. 7. Case 75,979. Negress. Age uncertain. About the sixth decade of life. Pictured the day of admission, December 31, 1932, when first seen by a physician. Positive sputum. Advanced bilateral pulmonary tuberculosis, with cavity-formation.

FIG. 8. Case 66,031. Negro. Age 30 years. Patient worked up to an hour before admission to hospital. Admitted to hospital March 26, 1931, in a state of collapse. Died in the hospital April 11, 1931. Positive sputum obtained on day of admission.

FIG. 9. Case 75,498. Negress. Age 25 years. Admitted to hospital November 23, 1932. Picture made on day of admission, when first seen by a physician. Positive sputum obtained on day of admission. Marked anaemia: R. B. C., 3,100,000; 70 per cent haemoglobin. Heavy infiltration, with multiple cavitation of the entire chest. Advanced bilateral pulmonary tuberculosis. Patient had been in and out of bed, with no permanent bed-rest, before being seen by a physician.

FIG. 10. Case 74,141. Negress. Age 16 years. Admitted to hospital August 25, 1932, and discharged September 1, 1932. No positive sputum obtained; but X-ray findings, constant elevation of temperature, and emaciation, with the physical findings, justified a diagnosis of pulmonary tuberculosis. Patient lived with a sister. Bed-ridden at the time these pictures were made, from pulmonary tuberculosis with positive sputum. Admitted to tuberculosis sanatorium, September, 1932; discharged December 31, 1932, at which time condition was quiescent.

FIG. 11. Case 73,284. Negro. Age 26 years. Admitted to hospital July 9, 1932, and discharged July 12, 1932. Lost 40 pounds between April, 1932, and June, 1932. Picture made the day patient was seen in Out-Patient Clinic by physician. Positive sputum obtained July 12, 1932. X-ray report: Advanced pulmonary tuberculosis, with cavity-formation. Patient gives period of disability as not exceeding two weeks. Patient was advised to enter tuberculosis sanatorium for treatment. Advice was declined. Patient preferred to return to his own home.

FIG. 12. Case 77,086. Negro. Age 35 years. Admitted to hospital March 31, 1933, and discharged March 24, 1933. Diagnosis: Pulmonary tuberculosis, bilaterial, with complicating laryngeal tuberculosis. Patient had been in the hospital in August, 1932, and diagnosis of pulmonary tuberculosis made at that time. There has been marked advancement in the disease in the interval. Sputum remains consistently positive. X-ray picture made March 21, 1933, shows bilateral pulmonary tuberculosis, but more marked on the right.

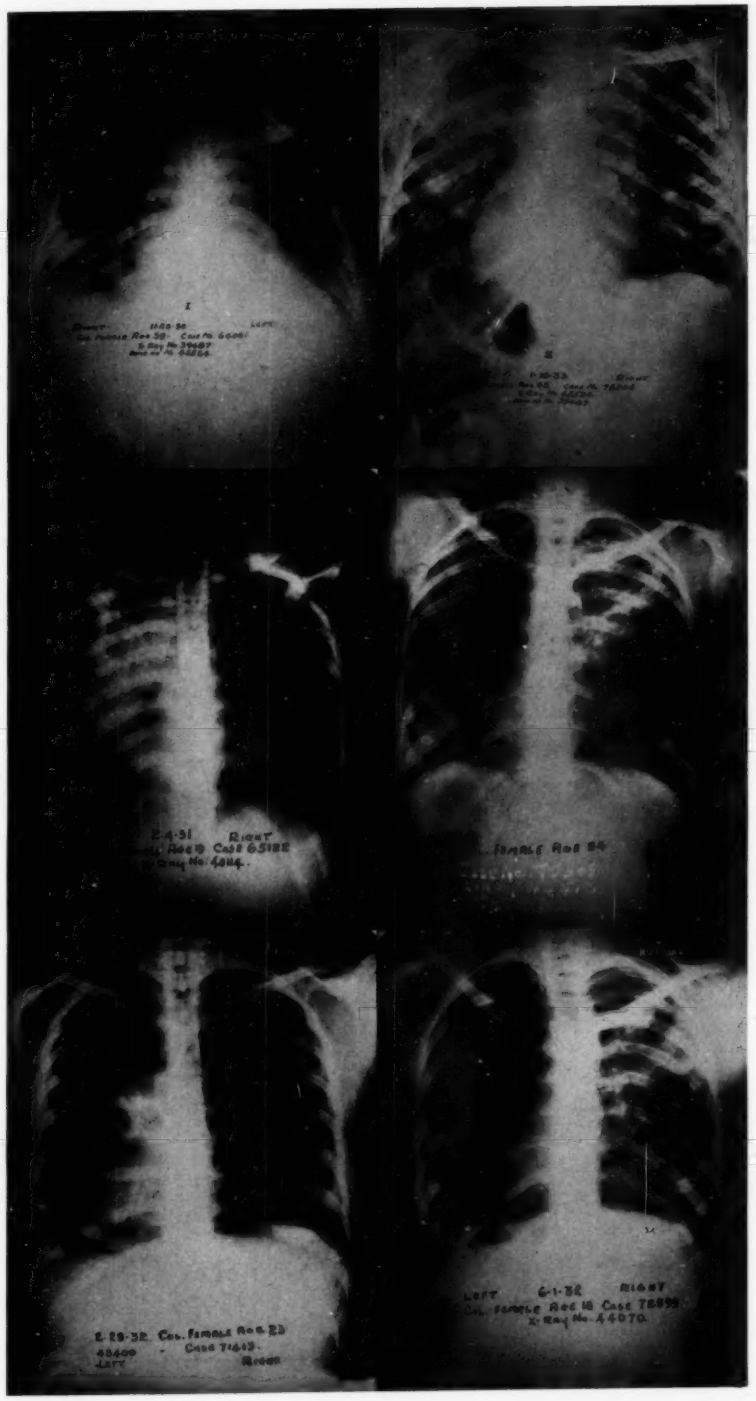

FIG. 13A

FIG. 13

FIG. 14

FIG. 15

FIG. 16

FIG. 17

FIG. 13A. Case 64,061. Negress. Age 40 years. Admitted to hospital November 22, 1930. This chest plate was made to define a postpartum pneumonia, and massive atelectasis, from which the patient made a recovery.

13B. Same patient, readmitted January 18, 1933 (case 76,206), on which date a second plate was made. Chest showed all evidences of widespread bilateral pulmonary tuberculosis, with cavitation. All specimens of sputum were positive for tubercle bacilli. X-ray plate showed extensive pulmonary tuberculosis of both lungs, with multiple cavity-formation of the left upper.

FIG. 14. Case 65,122. Negress. Age 19 years. Admitted to hospital February 4, 1931, and discharged February 15, 1931. History of having had pneumonia a month before. A week or two later developed cough and weakness. Sputum positive on day of admission. X-ray showed mottled consolidation of the entire right lung, indicating extensive pulmonary tuberculosis, with multiple cavitation.

FIG. 15. Case 73,508. Negress. Age 24 years. Admitted July 31, 1932, and discharged August 9, 1932. Sputum positive on day of admission. Marked secondary anaemia. X-ray revealed well-advanced pulmonary tuberculosis, with cavitation of right upper.

FIG. 16. Case 71,413. Negress. Age 23 years. Admitted to hospital February 27, 1932 and discharged March 3, 1932. Admitted with history of haemoptysis, cough, night-sweats for three weeks, and loss of appetite. Coughed up bright red fresh blood. No positive sputum obtained. X-ray plate showed extensive process in the left lung. Appearance is that of pulmonary tuberculosis.

FIG. 17. Case 72,599. Negress. Age 18 years. Admitted to hospital May 24, 1932 and discharged June 3, 1932. Patient's condition was discovered quite by accident, as patient was admitted because parents wished to have tonsils removed. Temperature on admission was 103°. Ran irregular high temperature during stay in hospital. Condition of tonsils discovered on examination at Out-Clinic 10 days before admission to hospital. X-ray revealed opacities, right upper: advanced active pulmonary tuberculosis, mostly on the right.

FIG. 18

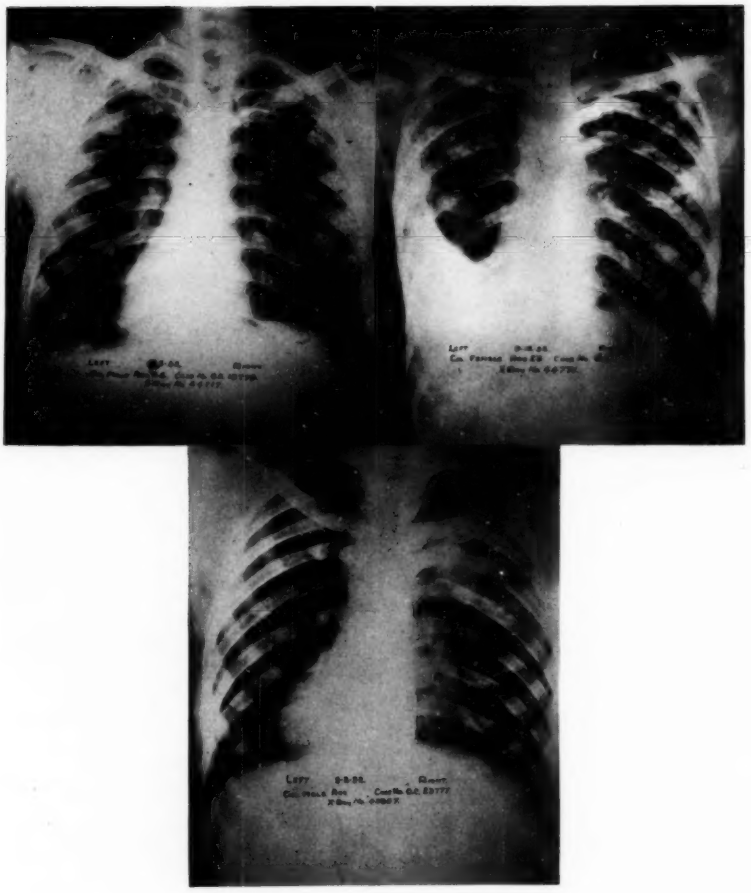

FIG. 19

FIG. 20

FIG. 18. Case 15,779 (O. C.). Negro. Age 23 years. Appeared at the Out-Clinic on account of haemorrhage, September 6, 1932. Admitted to hospital on same date and pictures made on this date also. Positive sputum obtained date of admission. Patient died August 9, 1933.

FIG. 19. Out-Clinic. Negress. Age 23 years. First seen at Out-Clinic on September 12, 1932 when X-ray plates were made. Died about June, 1933.

FIG. 20. Case 23,777 (O. C.). Negro. Age 31 years. X-ray picture made two weeks after first visit to Out-Clinic, when patient came in, complaining of stomach trouble. Complained of no symptoms relative to chest condition at all. Admitted to hospital May 9, 1932, with diagnosis of advanced pulmonary tuberculosis. Positive sputum obtained, May 10, 1932. X-ray report: "Advanced pulmonary tuberculosis with cavity-formation right upper."

TUBERCULOSIS AMONG NEGRO CHILDREN

With Special Reference to their Resistance to the Disease[1]

J. DONNELLY[2]

Tuberculosis in the Negro has been an important problem for many years in those sections of the country where the race is most numerous. In the Southern States, where a large proportion of the unskilled laborers and practically all the house-servants are recruited from the Negro population, the disease is a serious menace because of the closer contact between the white and Negro races and the consequent increased opportunities for the transmission of the infection. Usually the Negro death-rate from tuberculosis is two to three times as high as that of the white race; in some communities it is four times as high.

The following statistics of deaths from tuberculosis in the state of North Carolina in the years 1920 and 1932 may serve to illustrate the present status of the tuberculosis situation among Negroes. The population of this state is approximately two-thirds white and one-third Negro.

Year	*White deaths*	*White rate*	*Negro deaths*	*Negro rate*
1920	1,318	73.8	1,342	173.0
1932	861	37.6	1,146	122.2

Comparison of these figures shows that in the twelve year period (1920–1932) the yearly number of deaths among the whites has been reduced 457, or 34.66 per cent, while deaths among Negroes during the same period have been reduced only 196, or 14.6 per cent. The rate for the whites during this time has been reduced 49 per cent, whereas the Negro rate has been reduced only 29.3 per cent.

Conditions in most of the Southern States are similar to those in North Carolina. Hence tuberculosis in the Negro appears to be still a problem of considerable magnitude, particularly because of the continuing widespread infection of children. For this reason, a more intensive study of the incidence of the disease in both adults and children, and an increased

[1] Presented at a session of the Clinical Section at the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 15, 1934.

[2] Mecklenburg Sanatorium, Huntersville, North Carolina.

effort to safeguard children from repeated, and eventually overloading infections, are imperative.

In the limited literature on tuberculosis in the Negro "racial susceptibility," and the "absence of inherited or acquired immunity" to the disease are often stated as the reason for the high death rate in the race. It has long been the opinion of investigators that the Negro is inherently lacking in resistance to infection by the tubercle bacillus. The lack of the protection presumed to be afforded by childhood infection has been repeatedly advanced as the reason for this supposed absence of bodily resistance, even without adequate proof that first infection by the tubercle bacillus confers any appreciable immunity to reinfection.

Careful observation indicates that low resistance to tuberculosis in the Negro is far more apparent than real. It can be easily demonstrated that first infections in Negro children are taken care of quite as satisfactorily as in white children. Observation of actual cases also indicates that, in both the Negro adult and child, bodily resistance to the toxins of the tubercle bacillus is apparently greater than in the white race. Incidentally, the resistance of Negroes to other infections is worthy of note. It is well known to physicians familiar with disease among Negroes that, as a whole, they possess a remarkable resistance to severe pus infections. Also, in spite of the prevalence of syphilis in the race, locomotor ataxia, general paresis, and other conditions known to be of syphilitic origin are not at all common.

Severe tuberculous pulmonary involvement of the adult type seems to be slightly if at all more prevalent in Negro than in white children. Lymphatic involvement and haematogenous metastases, however, are much *more* prevalent. One very frequently sees in these children tuberculous suppuration of the cervical, axillary, or inguinal lymph nodes, and discharging sinuses caused by tuberculous involvement of the bones of the arm, ribs or sternum. Tuberculosis of the hip, knee and ankle is often seen, and tuberculous involvement of the skin is not uncommon. Negro children afflicted with such conditions do not usually appear to be otherwise ill, and numbers of them do not show tuberculous pulmonary involvement, although evidences of childhood-type disease are frequently present. Such types of infection were formerly explained as a result of implantation of infectious material on nonimmune soil. It is a fact, nevertheless, that similar types of infection are not often seen in white children, even though other tuberculous manifestations are alike in character in the children of both races.

The Negro child, although rendered allergic by first infection, apparently withstands frequently repeated infections with as definite a degree of success as the white child. In order to appreciate the many times multiplied opportunities for infection surrounding the Negro child, it is necessary to consider both the mental make-up of the adult Negro and certain environmental factors. Careful appraisal of these elements should be sufficient to cause one to wonder why the Negro death-rate from tuberculosis is not much higher than statistics show it to be.

Negroes were originally transported from their native habitat to this country as slaves. During their term of service as slaves health conditions among them were far more satisfactory than they have been since that time. Because they represented to their owners a certain monetary value, naturally the owners used every effort to safeguard their property. For this reason slaves were usually well-housed, well-clothed, well-fed, and were furnished medical care by their masters when necessary. During this period their death-rate from tuberculosis was approximately equal to that of the whites. After being freed numbers of them gravitated to the larger centres of population, where they were forced to undergo many hardships because of lack of employment, with its accompanying deficient food-supply and crowded, insanitary housing conditions. As a result, the death-rate from tuberculosis mounted rapidly, in 1885 reaching the high mark of 600 per 100,000. Although the death-rate has been much reduced since the tremendous rise which followed the Negro's first few years as a city-dweller, the environmental factors still exist to a large extent. Because of this fact the Negro death-rate from tuberculosis is still two to four times that of the whites. It is entirely reasonable to assume that the white race, living continuously in a similar environment, would fare no better, if as well. The majority of adult Negroes are uneducated, and, furthermore, they are lacking in the ambition to improve their environmental handicaps. It does not occur to them to desire or strive for the better things of life, the possibilities of to-morrow apparently being a matter of no great consequence. Their reaction to the effects of any disease is radically different from that which obtains in the white race. The Negro usually is not impressed by the prodromal symptoms of disease, rarely seeking medical advice until the pathological condition is well advanced. Tuberculosis is a disease in which prostration is not always extremely severe. Hence the disease is frequently far advanced in the Negro before he feels it necessary to seek some form of medical relief. When active disease is recognized,

an attempt to impress on the victim the seriousness of the condition usually produces no definite mental response. Often Negroes with far-advanced tuberculosis refuse to remain in sanatoria where they might receive sufficient benefit to at least prolong their lives. Death, unless immediately imminent, is to them a matter of slight consideration. Furthermore, it seems impossible to convince them that each case of tuberculosis is a serious menace to the health of other members of the immediate family.

Sensitiveness to bodily discomfort is far less acute in the Negro race than in the white. It is well known to physicians who have had experience in the medical and surgical treatment of Negroes that they are much less sensitive to pain than are the members of the white race. This racial difference may be due to the possibility that, in the process of evolutionary development, the nervous mechanism of the whites has become more highly organized and, consequently, more sensitive to stimuli than that of the Negro.

The Negro, as a rule, is firm in his belief that medicines will cure all human ills. Consequently, he will spend any part of his limited income for any worthless concoction which the vendor assures him will restore his health. Occasionally Negroes leave sanatoria because they believe that the medicines which, in their opinion, are necessary for their treatment, are purposely kept from them. Uneducated Negroes are peculiarly susceptible to the influence of religious fakirs and faith-healers, a characteristic which is a great handicap to the advancement of the race, and one which interferes materially with efforts in health education.

In combination with these racial characteristics, environmental factors are of no slight importance as a contributory cause of repeated infections of children. The Negro is primarily an unskilled laborer, or a tenant farmer, from both of which occupations the financial returns are always relatively small. Even if it were possible for him to lay aside any part of his meagre earnings for an emergency, he has no thought of the possibilities of the future. Low wages necessitate poor and crowded housing conditions with their accompanying inadequate sanitary facilities. For the same reason there is invariably an insufficient food-supply and insufficient clothing for the protection of the body from exposure. The Negro has no knowledge of food values, which fact prevents the obtaining of the most in food supply for the money expended. In spite of the fact that the Negro makes a satisfactory cook when trained by a white employer, food in the home usually is poorly prepared. Several other

factors which have an effect on physical resistance to disease in the adult must be added: namely, the prevalence of venereal disease, addiction to alcohol and drugs, and disregard of fatigue whatever the cause.

The recent extended period of unemployment and privation has already noticeably increased the effect of these environmental factors, much more noticeably than among the whites. The Negro, because he is an unskilled laborer and low wage-earner, first feels the effect of any reduction in employment. No employment with reduction of food-supply, frequently to the irreducible minimum, makes conditions, which at best were far from ideal, many times worse. The ultimate effect of such factors invariably requires a long time to reach the peak. Hence it is reasonable to assume that the incidence of tuberculosis in the Negro will rise for several years to come, because the opportunities for repeated infection of children are much increased by present hardships.

It has been assumed that the Negro is racially susceptible to infection by the tubercle bacillus, and that the disease is almost invariably rapidly progressive because of this racial susceptibility. We have also heard much concerning the seriousness of the first-infection type of tuberculosis in the Negro, but the evidence obtainable does not bear out this contention. That the absence of childhood infection by the tubercle bacillus is the reason for the apparent lack of resistance of the adult Negro to the disease, is a theory which is *not* supported by the facts. Childhood infection *does* occur in the Negro child as in the white child, and reinfection probably occurs many times more frequently.

From a consideration of these racial characteristics and environmental factors, which multiply the chances of the Negro child for repeated reinfections, it would seem that innate resistance of the Negro to the disease is far from lacking. Abundant evidence can be produced to prove that the Negro child handles first infections, and often reinfections, in a remarkably satisfactory manner.

Although many of the adult-type cases of tuberculosis in the Negro are far advanced when first seen, indicating the possibility of a very rapid progression, yet, when under observation in an institution, they frequently show a remarkable resistance to severe toxaemia over long periods of time. It is not unusual to observe maximum temperatures of 103° to 105°, with diurnal variations of 6° to 8°, continuing over periods of weeks, or even months. The quantity of toxins circulating in the blood-stream sufficient to cause these terrific reactions must necessarily be enormous. Evidence of severe toxaemia for such long

periods is not usually seen in tuberculosis in the white race. Extensive basal lesions with cavitation are just as likely to be found in the Negro as the same type lesions in the upper lobes. Furthermore, chronic tuberculosis with extensive production of fibrosis is comparatively rare in the Negro, advanced disease being usually of the cavernous type, even though it is frequently not rapidly fatal. The fact remains, however, that with the proper care and effort to prevent exogenous reinfections, the lives of even the far-advanced cases may be prolonged considerably. This certainly seems to indicate that natural resistance to the disease is far from lacking.

For the purpose of illustrating the possibility of extension of life by proper care even in far-advanced adult-type disease in Negro children, I wish to present the two following cases with the X-ray films. These films show clearly that the far-advanced adult-type disease from which these children were suffering was, in fact, a reinfection type.

Case 1: Negro school-girl, age 9 years. Admitted to sanatorium April 21, 1930; ill 4 or 5 months. Mother died from tuberculosis one year before. Weight on admission, 42 lbs. Considerable cough. Sputum positive for tubercle bacilli.

X-ray films taken on admission (figure 1) showed on the left a heavy opaque shadow from 3rd rib downward to base, with lighter fairly homogeneous shadow above 3rd rib. On the right side there was a considerable involvement of the childhood type with some calcification, indicating that the condition present was the reinfection type of disease. On the right, also, from about the 7th rib downward to the base there was an extensive area of heavy mottling.

For the first two months after admission the maximum daily temperature varied from 100.4° to 104°, and pulse-rate from 100 to 120, occasionally reaching 130. After this time until November, 1932, the maximum daily temperature reached 100° only three times, and the pulse-rate remained continuously below 100. The patient during that time remained practically free from symptoms, and gained 48 lbs. In May, 1933, the temperature rose again, and remained high until death which occurred November 15, 1933, three years and seven months after entering the sanatorium, and approximately 4 years from the beginning of her illness.

Figures 1, 2, 3, 4, 5, 6, and 7 indicate the course of the disease as shown in the X-ray films. Figures 2, 3, and 4 show, above the 2nd rib, large and definitely calcified areas indicating that this child had handled successfully probably several reinfections. The last film (figure 7) shows the terminal reinfection, a miliary-type disease. Change of environment and institutional care without doubt prolonged the life of this child, but such a result could not have been achieved without a remarkable resistance to infection.

Case 2: Negro school-boy, age 13 years, 11 months. Admitted to sanatorium July 12, 1930. Two years before admission mother had died from tuberculosis, and a few months prior to admission father died from the disease. Four years before this time aunt, also, had died from tuberculosis. Weight 92 lbs., and pulse-rate 90 to 100. Maximum daily temperature for six months after admission did not at any time exceed 100.4°. There was troublesome cough and the sputum was positive for tubercle bacilli.

X-ray films (figure 8) taken on admission showed advanced adult-type disease. In the right lung there was involvement of the childhood type with calcification, indicating that the present disability was undoubtedly caused by the reinfection type of disease. There was also fairly heavy mottling on the right from the extreme apex downward to the 4th rib. On the left there was heavy mottling from the apex almost to the base with a 3-cm. cavity in the apex. There was some evidence of fibrosis in the right lung.

This patient was put on bed-rest. In four months he had gained 21 lbs., but his weight then began to decline slightly. However, in March, 1932, he weighed 114 lbs., a net increase of 22 lbs. Maximum daily temperature remained 100° or less for 18 months following admission, after which time he began to have frequent rises to 103°–104° for several-day periods. He died April 17, 1933, two years, nine months and five days after his admission to the sanatorium.

Two brothers and two sisters of this boy, ranging in age from 7 to 13 years, had violently positive skin-reactions. The X-ray films showed extensive childhood-type disease in the two younger children and adult type in the two older. The older girl, who was not sent to an institution, but remained in her old environment, died within 5 months. It seems reasonable to assume that removal of the older boy from his home together with institutional care prolonged his life materially, in spite of the fact that his disease was far advanced when first recognized.

In March, 1932, we skin-tested 1,259 white and 400 Negro school-children; and in January, 1934, approximately two years later, 2,248 whites and 408 Negroes. The test used was the Mantoux intracutaneous of 0.1-mgm. strength. The total number of cases in these two series is too small to justify any definite conclusions, but there are several points which are at least significant.

In the 1932 series, 277 white children, or 22 per cent, and 99 Negroes, or 24.75 per cent, showed positive skin-reactions. In the 1934 series 431 white children, 19.12 per cent, and 82 Negroes, 20.1 per cent, were positive reactors. As will be noted, the total number of reactors among the white children was approximately 3 per cent less in 1934 than in 1932,

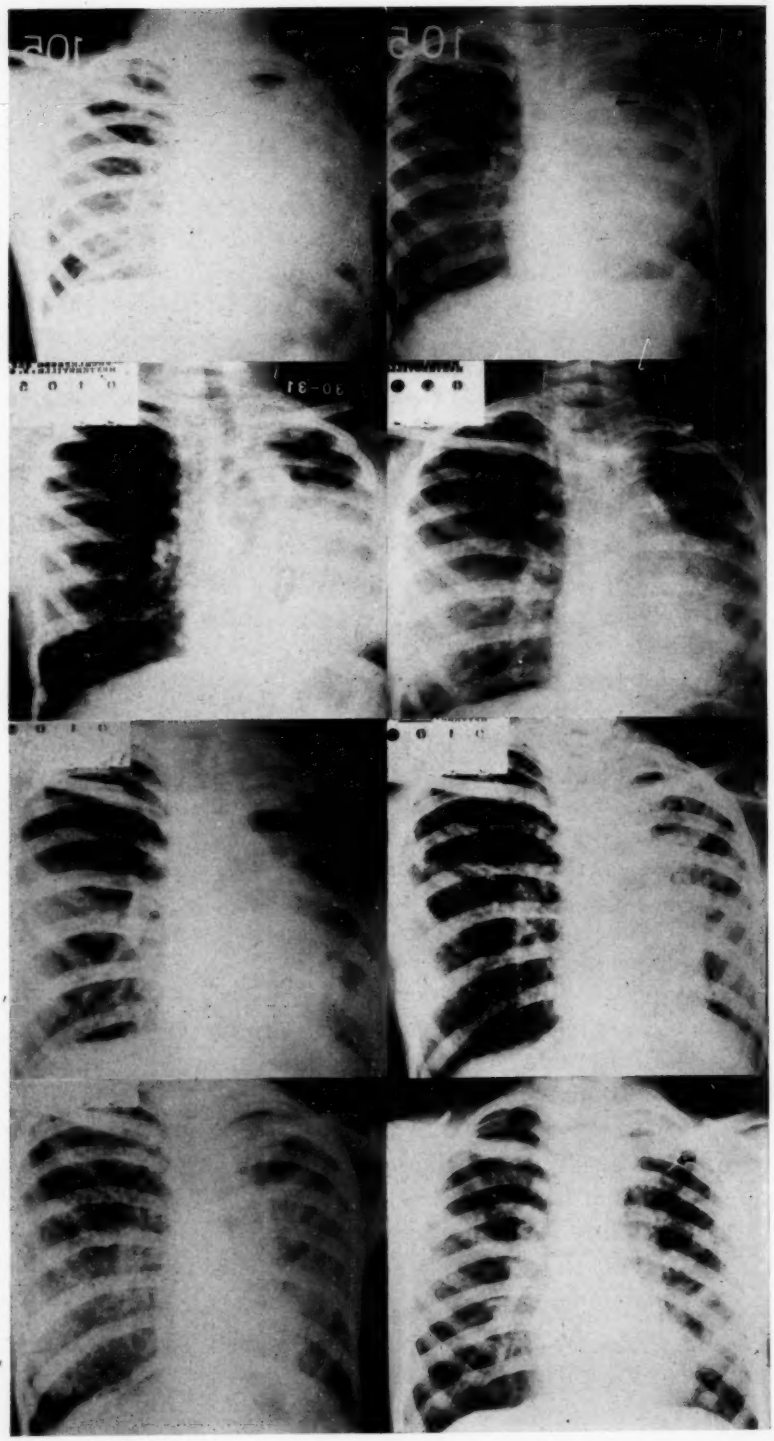

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIG. 7

FIG. 8

and nearly 5 per cent less among the Negroes. However, the following figures on the degree of violence of the reactions may be of interest.

	White (1932)		*Negro (1932)*	
	Number	*Per cent*	*Number*	*Per cent*
1- and 2-plus.....	186	67.16	40	40.4
3- and 4-plus.....	91	32.84	59	59.6

A similar computation for the 1934 series is as follows:

	White (1934)		*Negro (1934)*	
	Number	*Per cent*	*Number*	*Per cent*
1- and 2-plus.....	348	80.74	31	37.8
3- and 4-plus.....	83	19.26	51	62.2

It is somewhat surprising that, in spite of widespread unemployment during the intervening two years, with the consequent hardships undergone by the majority of these children, the percentage of positive reactors should be so definitely reduced in 1934. However, it will be noted that, although the 3-plus and 4-plus reactors among the white children in 1934 were 13.58 per cent less than in 1932, among Negroes these stronger reactions were 2.6 per cent higher in 1934 than in 1932. It is also to be noted that among the Negroes the more violent reactors comprise the greater proportion of the total number, 59.6 per cent in 1932 and 62.2 per cent in 1934.

Since the tuberculin skin-test is presumably a test for allergy, it is apparent from the much higher percentage of violent reactions that a greater proportionate number of the Negro children was more definitely allergic. This higher incidence of the stronger reactions was probably due not only to more frequent reinfections, but also to more recent infections.

FIG. 1. Case 1. Negro girl, age 9 years. Far-advanced bilateral adult-type disease. April 21, 1930.

FIG. 2. Case 1. Childhood type, right hilum. Calcification left apex. Some clearing left lung. May 28, 1930.

FIG. 3. Case 1. Calcification left upper. Contraction left lung. Some clearing right lower. September 30, 1931.

FIG. 4. Case 1. Further clearing left lung. Some extension of process in right lower. December 9, 1931.

FIG. 5. Case 1. Extension of process in both lungs. November 26, 1932

FIG. 6. Case 1. Miliary terminal infection. September 15, 1933

FIG. 7. Case 1. Miliary terminal infection. November 3, 1933

FIG. 8. Case 2. Negro boy, age 13 years. Far-advanced adult type. Cavity left apex. Evidence of old childhood-type disease. July 12. 1930.

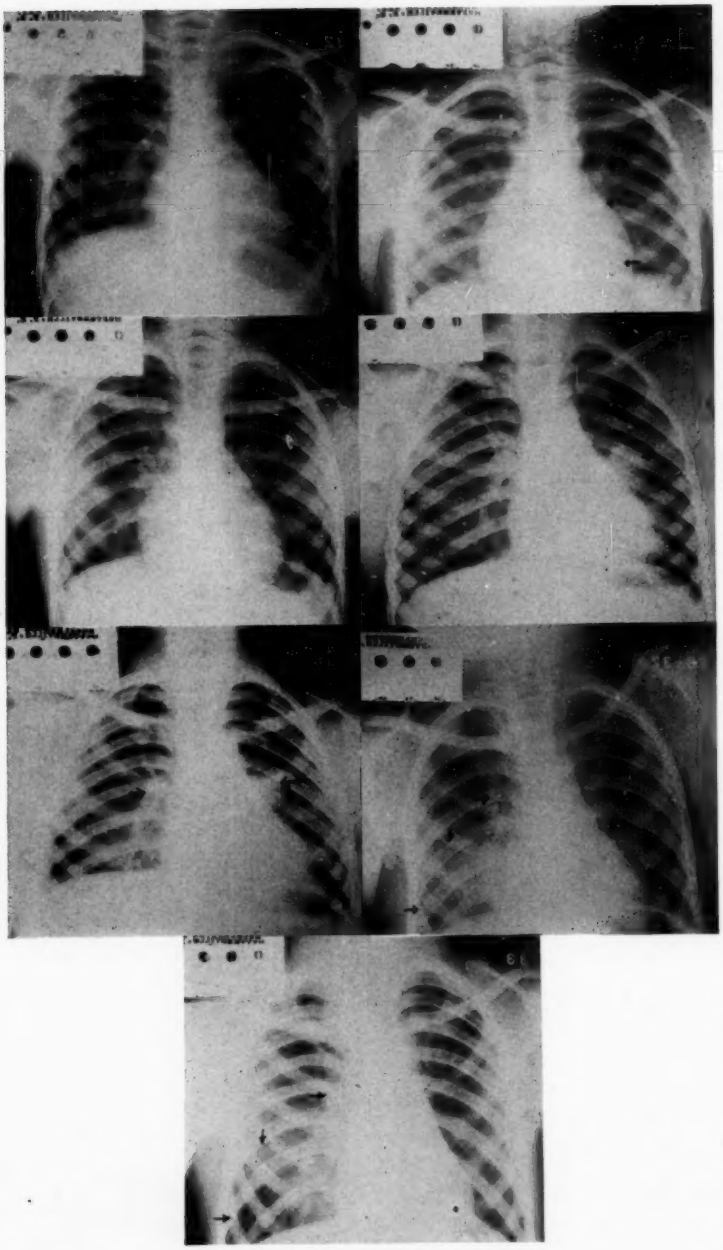

FIG. 9

FIG. 10

FIG. 11

FIG. 12

FIG. 13

FIG. 14

FIG. 15

We have not been able to obtain X-ray films of the Negro children in the 1934 series at the time this is written, but the following is a tabulation of those with definite lesions by X-ray in the 1932 series.

	White	*Negro*
Number	47	35
Percentage of positive reactors	16.96	35.35
Percentage of total number	3.65	8.07

Of the 47 cases among the white children with definite lesions by X-ray only 2 were of the adult type, and of the 35 Negro children with definite lesions only 3 were of the adult type.

The X-ray films of several of the cases of diseased Negro children in this short series may be of interest. They demonstrate the degree of resistance to infection often possessed by the very young of this race, even under adverse circumstances. The evidence of improvement in the last 3 cases is the more noteworthy, because they were forced to remain in their old environment, and were very probably subjected to repeated reinfections. Although unable to care for them in an institution, we have attempted to keep them under observation in order to observe the course of their disease.

Case 3: Negro girl, age 5 years. Contact. No symptoms. Positive skin-test. X-ray film (figure 9), taken May 5, 1932. Definitely calcified areas at both hila.

Case 4: Negro boy, age 6 years. Contact. No symptoms. Positive skin-test. X-ray film (figure 10), taken June 3, 1932. Considerable calcification around left hilum. Ghon tubercle-formation just above diaphragm on both sides.

FIG. 9. Case 3. Negro girl, age 5 years. Calcification both hila. May 6, 1932

FIG. 10. Case 4. Negro boy, age 6 years. Calcification left hilum. Ghon tubercle at edge of heart shadow, left side, just above diaphragm. June 3, 1932.

FIG. 11. Case 5. Negro boy, age 8 years. Numerous small calcified areas both hila. June 3, 1932.

FIG. 12. Case 6. Negro boy, age 8 years. This first film shows extensive childhood-type disease. June 17, 1932.

FIG. 13. Case 6. Film taken 16 months later shows increased calcification on left side. October 13, 1933.

FIG. 14. Case 7. Negro boy, age 7 years. First film shows childhood-type disease and infiltration in left lower. November 26, 1932.

FIG. 15. Case 7. Second film shows clearing of parenchymal lesion with formation of fibrous tissue. October 18, 1933.

Case 5: Negro boy, age 8 years. Contact. No symptoms. Positive skin-test. X-ray film (figure 11), taken June 3, 1932. Numerous small calcified areas both hila.

Case 6: Negro boy, age 8 years. Contact. No symptoms. Positive skin-test. First X-ray film (figure 12), taken June 17, 1932, showed extensive childhood-type tuberculosis. Second film (figure 13), taken October 18, 1933, shows considerable calcification in the lesion on the left.

Case 7: Negro boy, age 7 years. Contact. No symptoms. Positive skin-test. First X-ray film (figure 14), taken November 26, 1932, showed childhood-type tuberculosis and a flocculent infiltration in the left base, extending

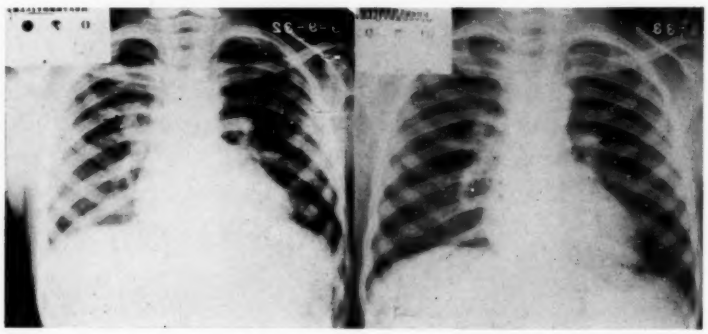

FIG. 16 FIG. 17

FIG. 16. Case 8. Negro boy, age 5 years. First film shows extensive childhood-type disease with some calcification. September 9, 1932.

FIG. 17. Case 8. Second film shows considerable increase in calcification. October 25, 1933.

outward to the periphery. A second film (figure 15), taken October 18, 1933, shows considerable clearing of the parenchymal infiltration with formation of fibrous tissue.

Case 8: Negro boy, age 5 years. Contact. No symptoms. Positive skin-test. First X-ray film (figure 16), taken September 9, 1932, shows fairly extensive childhood type disease with some calcification. Second film (figure 17) taken October 25, 1933, shows considerable increase in the calcification and no noticeable extension of the remaining apparently active areas.

The pathological conditions shown in the films seem to indicate that these children do *not* belong to a race which is nonresistant to infection

by the tubercle bacillus. All of the children are pure blacks, and hence admixture with white blood cannot be advanced as a theory for their resistance to disease. Many similar cases can be cited to disprove the statement that childhood infection does *not* occur in Negroes. Such material leads one to doubt seriously that childhood infection by the tubercle bacillus affords any great degree of protection against the disease in later life. In fact, in many X-ray films of advanced disease in the adult Negro definite evidence of calcified childhood-type disease can be seen. If the Negro were racially susceptible to tuberculosis such healing processes as are evident in these films would not occur. Furthermore, if childhood infection afforded any great degree of protection against reinfection, extensive subsequent disease in the Negro would be relatively infrequent. The contrary, however, is the rule. Many Negro families give no history of tuberculosis for generations, as far as such histories can be authenticated, although their environmental surroundings would tend to spread infection if it were present. Many individual members of the race escape the manifestations of the reinfection type of disease, even though undoubtedly frequently exposed to infection. These facts would seem to indicate that Negroes are *not* racially susceptible to the disease.

It is imperative that every possible effort be made to prevent any further rise in the incidence of tuberculosis in this race. Because of the more or less close contact between the white and Negro races in certain sections, protective efforts will be for the betterment of health conditions in both races. It is impossible to prevent first infections in many Negro children, because of the ignorance and carelessness of adults with active disease. Results, however, may be obtained by the prevention of overloading reinfections. Sanatorium treatment of the adult tuberculous Negro is, as a rule, most unsatisfactory, because of his racial characteristics. Also, the education of the adult Negro in matters pertaining to health appears to be hopeless for the same reason. Since the Negro child possesses the ability to take care of even repeated infections with a fair degree of success, a considerable number will recover if the contact is permanently broken. A great many of them do obtain an arrest of their disease in their old environment. Nothing can be gained, however, if a child is treated in an institution until his disease is arrested, only to be returned to his home to be reinfected.

In view of the fact that first infections by the tubercle bacillus apparently do not protect against reinfections, the possibility of producing

individual immunity to the disease among Negroes seems to be decidedly remote. The reduction of the incidence of tuberculosis in the Negro race, as in the white, will depend upon the prevention of infection. Many more sanatorium beds for the care of adult cases, accommodations for the institutional care of infected children, and efforts toward improvement of the environmental conditions surrounding the Negro are the present necessities.

It has been characteristic of the Negro in the South since his slave-time ancestors to depend on his white neighbors for assistance in finding a solution for all his problems. Therefore it becomes necessary for the white race to consider the matter seriously and provide the means. It is to be hoped that the Negro may receive more assistance in the future in solving his tuberculosis problem than he has in the past.

LARYNGOPULMONARY TUBERCULOSIS

A Review of Twenty Years' Experience[1]

JULIUS P. DWORETZKY[2]

The purpose of this paper is twofold: first, to emphasize a few observations on laryngopulmonary tuberculosis based on an experience of twenty years in this field; and, second, to give a recent statistical study of the occurrence of laryngeal involvement in a series of 500 cases of pulmonary tuberculosis.

Tuberculosis of the larynx should be considered as a complication of pulmonary tuberculosis and should never be regarded as a clinical entity. *Laryngopulmonary tuberculosis* is, therefore, a more descriptive and fitting term for this manifestation of tuberculosis, and it is in the above sense that it shall be employed.

DIAGNOSIS

The fact that tuberculosis of the larynx is usually secondary to pulmonary tuberculosis is well established and generally accepted. We have all had the experience of finding what appears, on clinical examination, to be a primary laryngeal lesion; but, were these cases sufficiently and properly investigated with the assistance of X-ray films and laboratory work, a primary focus of infection would invariably be found in the lungs. When, after most thorough search, an infection in the lungs cannot be found, a diagnosis of laryngeal tuberculosis is in my opinion rarely justified. Personally, I never saw a case of primary laryngeal tuberculosis.

My observation has been that laryngeal tuberculosis occurs only in cases of active pulmonary tuberculosis: a positive sputum at some time in the course of the disease is nearly always present, and, if the sputum is persistently negative, a diagnosis of laryngeal tuberculosis should be held in abeyance. In cases in which the pulmonary lesion has become definitely arrested, the occurrence of laryngeal tuberculosis is highly improbable.

[1] Read at the fortieth annual session of the American Laryngological, Rhinological and Otological Society, Charleston, South Carolina, April 4, 1934.

[2] Liberty, New York.

The diagnosis of laryngeal tuberculosis is usually a simple matter for the phthisiologist. Once a diagnosis of pulmonary tuberculosis has been established and a laryngoscopic examination yields the usual objective pathological findings, the diagnosis becomes evident. With the laryngologist, however, the problem is a more difficult one, and considerable caution must be exercised before arriving at an accurate diagnosis. As stated, a diagnosis of laryngeal tuberculosis should be made only when an existing pulmonary lesion has been definitely demonstrated. Just as the phthisiologist's examination should not begin at the apices of the lungs, neither should the laryngologist's examination end with the larynx. The respiratory tract extends from the anterior nares to the bases of the lungs, and a patient complaining of symptoms referable to any part of the respiratory tract should have the entire system explored. Before definitely arriving at a laryngeal diagnosis the laryngologist should have a complete report of the chest findings and thus avoid many diagnostic pitfalls. Furthermore, by bearing in mind that a positive sputum some time in the course of the disease is practically essential for a diagnosis of tuberculosis of the larynx, other conditions or affections causing similar pathological changes in the larynx can readily be ruled out. Of course it must be remembered that tuberculosis patients may have non-tuberculous lesions in the larynx, as brought out by J. B. Greene (1) in a most excellent paper presented before the American Laryngological Society in 1929. In such cases a differential diagnosis sometimes becomes difficult.

CLINICAL TYPES

In a paper written in 1916 (2) I classified laryngeal tuberculosis in three clinical groups: acute, subacute and chronic; depending on the pathological involvement and the course of the disease. After nearly twenty years of experience in this field I still feel that this classification or clinical grouping is a most practical guide and especially as far as prognosis and treatment are concerned.

PROGNOSIS

It is not advisable to make a prognosis as to life or voice of a patient by a laryngoscopic examination alone. No matter how slight the laryngeal lesion may be, if the pulmonary lesion is of the severe and rapidly progressive type the prognosis is necessarily poor. On the other hand, if the pulmonary lesion is of the productive type or else takes on a favorable

course because of instituted treatment, even severe laryngeal lesions often heal. The following factors should be considered before venturing a prognosis:

1: Character of the pulmonary lesion: Patients with tuberculosis of the productive type fare better than those with the exudative or the caseous-pneumonic type.

2: Extent of pulmonary lesion: The less-advanced cases always present a better prognosis than those in the advanced stages, in which a great deal of destruction of tissue has occurred.

3: Type and extent of laryngeal lesion: In the acute type the prognosis should always be guarded. Here the lesion may become peracute, with rapid destruction of the tissues of the larynx and with perichrondritis. This type is often complicated by tuberculosis of the pharynx, soft palate and tonsils, and the patient dies within six or twelve weeks from inanition and severe toxaemia. Or, the disease may run a less severe course than the peracute, showing a slight tendency to fibrosis. These patients usually suffer from marked hoarseness or aphonia and a great deal of irritation in the larynx with constant desire to expectorate. Dysphagia is of common occurrence and may be very pronounced depending largely on the location of the lesion. In this type the prognosis is generally unfavorable and the patient's length of life is considerably curtailed. The acute manifestation often occurs as a terminal condition in patients with advanced pulmonary tuberculosis. In subacute cases the prognosis is much better. This is the type that is most amenable to local treatment, and when other factors are favorable the prognosis is good. In the chronic type of cases the prognosis is most hopeful. Here the voice may remain affected but the length of the patient's life is generally not influenced. The extent of the lesion does not necessarily influence the prognosis as to life, although cases of slight involvement are the most hopeful ones as far as the voice is concerned.

4: Location of the lesion: The prognosis as to life is most favorable in cases in which the lesion is situated at the posterior commissure or at the true vocal cords. Lesions of the epiglottis, aryepiglottidean folds, and arytenoids and ventricular bands usually present a less favorable prognosis.

5: Early diagnosis: It is evident that the earlier a diagnosis is made the more easily can the lesion be cured or checked in its progress.

6: Character of treatment and its early application: Cases suitable for collapse therapy present a much better prognosis than those in which collapse therapy cannot be employed. The sooner treatment is applied, the more hopeful is the outlook in the average case.

7: Complicating intercurrent diseases: Conditions such as diabetes, syphilis, gastroenteritis, etc., render the prognosis more serious.

8: The general condition of the patient: This is an important factor in making a prognosis and should be taken into consideration.

TREATMENT

Since laryngeal tuberculosis is secondary to tuberculosis of the lungs, our main object should be to treat the pulmonary lesion first. In discussing the methods of treatment, it is well to remember that conservatism still governs the treatment of pulmonary tuberculosis. This should especially apply to tuberculosis of the larynx. I believe that we can all recall the time, perhaps as recently as two decades ago, when surgery was commonly practised on the tuberculous larynx. Such procedures at the present time, I believe, have been almost entirely abandoned, and the tendency in all tuberculosis institutions as well as in the clinics is to concentrate primarily on the pulmonary lesion. In other words, while the scope of thoracic surgery is becoming wider, surgery of the larynx is now being limited to the exceptional cases.

The treatment of laryngopulmonary tuberculosis is (1) preventive; (2) general, or indirect; and (3) local, or direct.

(1) Preventive treatment: Since it is definitely accepted that active pulmonary tuberculosis is the direct aetiological factor of laryngeal tuberculosis, the prevention of this complication can be undertaken along definite lines. Every patient suffering from active pulmonary tuberculosis with a positive sputum should be considered as a potential case of laryngeal tuberculosis, and whenever we succeed in arresting the pulmonary lesion we are definitely preventing the occurrence of laryngeal tuberculosis. It behooves us, therefore, to resort to every possible measure in order to bring about the healing of the pulmonary lesion. Time does not permit us, nor is it within the scope of this paper, to describe the treatment of pulmonary tuberculosis. However, I feel that it is pertinent to mention some of the most important developments which have been made within the past ten or fifteen years in the treatment of this disease, and I am referring to collapse therapy. I believe that collapse therapy, successfully applied in properly selected cases of pulmonary tuberculosis, invariably prevents the occurrence of laryngeal tuberculosis. This was definitely demonstrated in 1930 (3), when I presented a paper before this Society. At that time I collected 5,382 cases of pulmonary tuberculosis in which collapse therapy had been employed by various phthisiologists in the United States, and in only twelve of these did laryngeal tuberculosis develop; and in these 12 cases the collapse was inadequate to arrest the disease.

In addition to attacking the pulmonary lesion, abnormal conditions in the upper air-passages, such as nasal obstruction causing improper breathing or improper drainage, inflammatory conditions in the nasopharynx or pharynx, diseased or infected tonsils, the excessive use of tobacco or alcohol, or excessive use of the voice, will often cause a catarrhal condition in the larynx and thereby lower the local resistance of the larynx. Such abnormal conditions, whenever possible, should be corrected.

(2) General treatment: This treatment should be directed mainly at the pulmonary lesion and the general condition of the patient. Each case should be individualized and the pulmonary lesion should be given intensive study. It must be remembered that the primary object, in complicated as well as uncomplicated cases of pulmonary tuberculosis, is to attain an arrest of the pulmonary lesion. The proper measures should therefore be employed. Bed-rest is still our mainstay in the treatment of tuberculosis, but, in addition, if the case presents definite indications for collapse therapy, the same treatment should be immediately applied. Heretofore, the presence of laryngeal tuberculosis served as a contraindication to the induction of pneumothorax or any other form of collapse therapy. From studies made in 1925 and 1930, which I presented before the Triological Society, and also from subsequent observations, I feel convinced that the presence of laryngeal tuberculosis should never be considered as a contraindication to the application of collapse therapy but should make the indications for this form of treatment so much more urgent. Every effort should be made to build up the patient's resistance. The gastrointestinal tract should receive primary attention. Complicating diseases, such as diabetes, syphilis, or other disabilities, should be taken care of in the usual manner.

(3) Local or direct treatment: Here *vocal rest* is of primary importance, especially if the laryngeal lesion is of the acute or subacute type. Chronic lesions do not seem to be harmed through the moderate use of the voice.

Cauterization is the method of choice and especially when the lesion is more or less localized. It promotes fibrosis and healing and often relieves pain. Here, I should like to quote Sir St Clair Thomson, who in an article on the treatment by galvanocautery states: "As a local help the galvano-cautery is the most valuable remedy we possess at present. The cases in which it is suitable are relatively few, but these cases, well selected, yield a cure in a large proportion of cases" (4). When cauterization is insufficient to relieve dysphagia, blocking of the internal branch of the superior laryngeal nerve with alcohol is often of value.

In this way relief may be obtained for several weeks and sometimes months.

Heliotherapy has been used with reported success. Personally I have never had any experience with it. Here, too, I should like to quote Sir St Clair Thomson, who made a study of the effects of artificial-sunlight

TABLE 1

400 Otisville cases

	MEN		WOMEN		COMBINED	
		per cent		*per cent*		*per cent*
	237	59.3	163	40.7	400	100
Clinical diagnosis:						
Stage i	41	17.3	63	38.7	104	26
Stage ii	167	70.5	85	52.1	252	63
Stage iii	29	12.2	15	9.2	44	11
	237	100	163	100	400	100
Sputum:						
Positive	167	70.5	105	64.4	272	68
Negative	70	29.5	58	35.6	128	32
	237	100	163	100	400	100
Larynx:						
Positive	35	14.8	15	9.2	50	12.5
Negative	202	85.2	148	90.8	350	87.5
	237	100	163	100	400	100
Sputum in 50 cases of laryngopulmonary tuberculosis:						
Positive	33	97.1	16	100	49	98
Negative	1	2.9	0		1	2
	34	100	16	100	50	100
Treatment:						
Routine	201	85	129	79.8	330	82.5
Collapse therapy	36	15	34	20.2	70	17.5
	237	100	163	100	400	100

treatment, with carbon lamps obtained from Copenhagen, which were exactly similar to those used and recommended in the Finsen Institute. In summarizing his observations Sir St Clair Thomson states that "In thirty-two favorable cases of laryngeal tuberculosis, there were no striking evidences of benefit from light treatment. In only two or three might some help from it be claimed. . . . Quite as good results have been

obtained and just as swiftly with voice rest sometimes supplemented with galvano-cautery or artificial pneumothorax and in all cases the sanatorium regime." He then goes on to say that "While it may appear to be of help in a very few cases it probably acts only by suggestion; that it is fraught with danger if not scrupulously supervised; and

TABLE 2

100 private cases

	MEN		WOMEN		COMBINED	
		per cent		*per cent*		*per cent*
	60	60	40	40	100	100
Clinical diagnosis:						
Stage i	9	15	0		9	9
Stage ii	11	18.3	11	27.5	22	22
Stage iii	40	66.7	29	72.5	69	69
	60	100	40	100	100	100
Sputum:						
Positive	52	86.7	38	95	90	90
Negative	8	13.3	2	5	10	10
	60	100	40	100	100	100
Larynx:						
Positive	12	20	11	27.5	23	23
Negative	48	80	29	72.5	77	77
	60	100	40	100	100	100
Sputum in 23 laryngopulmonary cases:						
Positive	12	52.2	11	47.8	23	100
Negative	0		0		0	
	12	52.2	11	47.8	23	100
Treatment:						
Routine	45	75	25	62.5	70	70
Collapse therapy	15	25	15	37.5	30	30
	60	100	40	100	100	100

that on the whole in patients in a well ordered sanatorium it is no addition to the treatment at present in use" (5).

Local medication: I have tried nearly all advocated remedies. At one time I thought that a solution of iodine in glycerine applied directly to ulcerated areas was of value. I am frank to admit that I have abandoned the use of local medication except in rare cases. Sprays, consisting of menthol, oil of chaulmoogra and albolene, will often relieve patients of

a great deal of discomfort in the larynx and may be used freely by the patient himself.

TABLE 3

500 cases combined

	MEN		WOMEN		COMBINED	
		per cent		*per cent*		*per cent*
	297	59.4	203	40.6	500	100
Clinical diagnosis:						
Stage i	50	17	63	31.1	113	22.6
Stage ii	178	59.9	96	46.8	274	54.8
Stage iii	69	23.1	44	22.1	113	22.6
	297	100	203	100	500	100
Sputum:						
Positive	219	73.8	143	70.4	362	72.4
Negative	78	26.2	60	29.6	138	27.6
	297	100	203	100	500	100
Larynx:						
Positive	47	15.8	26	12.9	73	14.6
Negative	250	84.2	177	87.1	427	85.4
	297	100	203	100	500	100
Sputum in 73 laryngopulmonary cases:						
Positive	47	98	25	100	72	98.7
Negative	1	2	0		1	1.3
	48	100	25	100	73	100
Treatment:						
Routine	246	83.8	154	75.7	400	80
Collapse therapy	51	16.2	49	24.3	100	20
	297	100	203	100	500	100
Clinical diagnosis of 73 laryngeal tuberculosis cases:	5	10.4	3	12	8	10.9
Pulmonary stage i	28	58.3	9	36	37	50.7
Pulmonary stage ii	15	31.3	13	52	28	38.4
Pulmonary stage iii	48	100	25	100	73	100

ANALYSIS OF 500 CASES OF PULMONARY TUBERCULOSIS, EXAMINED AT THE OTISVILLE SANATORIUM IN 1934, COMPARED WITH 500 CASES EXAMINED IN 1914

In 1914, while resident physician on the staff of the New York Municipal Sanatorium at Otisville, New York, I examined 500 cases of pulmonary tuberculosis with special regard to the incidence of laryngeal com-

plications, and presented my findings before the New York Academy of Medicine (6). I made a similar study during the past six months, based on the examination of the same number of adult patients at the same institution and the findings are shown in the appended tables.

Before presenting the tables, however, I wish to state that the policy of

TABLE 4

Comparative analysis of 500 cases of pulmonary tuberculosis

	1914		1934	
		per cent		*per cent*
Pulmonary diagnosis:				
Stage i	124	24.8	113	22.6
Stage ii	303	60.6	274	54.6
Stage iii	73	14.6	113	22.6
	500	100	500	100
Sputum in 470 pulmonary cases:			*500 cases*	
Positive	332	70.6	362	72.4
Negative	138	29.4	138	27.6
	470	100	500	100
Larynx:				
Positive	128	25.6	73	14.6
Negative	372	74.4	427	85.4
	500	100	500	100
Sputum in 128 laryngopulmonary cases:			*73 cases*	
Positive	116	91	72	98.6
Negative	12	9	1	1.4
	128	100	73	100
Incidence of tuberculous laryngitis in various pulmonary stages:				
Pulmonary stage i	(15 in 124)	12	(8 in 113)	7.1
Pulmonary stage ii	(80 in 303)	26.5	(37 in 274)	13.5
Pulmonary stage iii	(33 in 73)	45.3	(28 in 113)	24.8
Treatment:				
Routine	500	100	400	80
Collapse therapy	0	0	100	20
	500	100	500	100

the Otisville Sanatorium has been more or less the same during the past twenty years; namely, to admit cases of the more favorable type, that is, the early and moderately advanced but only a few of the advanced cases, and preferably those suitable for collapse therapy. The population of Otisville Sanatorium has been reduced to about 400. I have, therefore,

added one hundred consecutive cases from my private practice, bringing the total up to 500, the same as in 1914. The policy as to treatment at the Otisville Sanatorium, however, has been changed a great deal during the past twenty years, namely, the rest cure is very much more emphasized, and patients are not allowed to do any work whatsoever. In addition to this, collapse therapy, while it was not at all practised in 1914, is now applied in about 20 per cent of the cases.

SUMMARY AND CONCLUSIONS

1. Tuberculosis of the larynx should be considered as a complication of pulmonary tuberculosis and should never be regarded as a clinical entity.

2. The treatment of laryngopulmonary tuberculosis should consist mainly of the treatment of the parent lesion, which is the pulmonary disease.

3. Collapse therapy, which is the most valuable measure in the treatment of pulmonary tuberculosis, when successful, will not only prevent the development of laryngeal tuberculosis but will also promote healing of a coexisting laryngeal lesion.

4. A group of 500 cases of pulmonary tuberculosis was examined twenty years ago. Whereas, the incidence of laryngeal tuberculosis in 1914 was 25.6 per cent, the incidence in 1934 was found to be 14.6 per cent.

5. This pronounced reduction in the frequency of the occurrence of laryngeal tuberculosis can readily be explained by the improved methods of diagnosis and the consequent earlier application of treatment; also by the improved methods of treatment. Whereas collapse therapy was not employed in any of these cases in 1914, it was employed in 20 per cent of the cases of the present group.

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PULMONARY SYPHILIS

With a Report of a Case[1]

M. JACOBS

The subject of syphilis of the lung affords opportunity for considerable study, first, by reason of its rarity, and, second, because of the infrequency of its recognition. The latter phase of the subject is due to the fact that it is conceded to be a most difficult diagnosis to determine, even by postmortem examination. Consequently, its confusion with other morbid conditions of the lungs, particularly aberrant tuberculosis, is by no means uncommon.

The rarity of this disease may be gained from the information that, out of 2,800 autopsies performed at the Johns Hopkins Hospital (1), four of these presented characteristic tertiary pulmonary syphilis. Of the 1,200 patients referred to the tuberculosis wards of the Jefferson Hospital, McCrae and Funk (2) diagnosed 72 cases as nontuberculous, and four were considered pulmonary syphilis. From an enormous number of cases surveyed, J. K. Fowler (3), of the London Museum, discovered 12 cases of lung syphilis, but, of these, two were of doubtful nature. Lord (4) reviewed 3,000 postmortems and found one case of pneumonitis of syphilitic origin. Karshner and Karshner (5) believe that syphilis of the lung cannot be established antemortem. Denman (6) states that the pathology of pulmonary syphilis is very complicated and the clinical picture is not characteristic. Hartung and Freedman (7), in reporting three cases of pulmonary syphilis, claim that the clinical diagnosis is extremely difficult and fraught with danger.

In recent years a number of clinicians have reported more and more clinical observations of pulmonary syphilis, though hestitating to make this diagnosis. Many have reported their cases as "pulmonary disease in the syphilitic," or "syphilis with pulmonary manifestations," or "suspected pulmonary syphilis." The physical findings in these cases are similar to the findings encountered in cases of pneumonia or bronchopneumonia in a chronic or subacute form, or to the findings in cases of chronic pleurisy or thickened pleura.

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While there are cases of acute fulminating syphilis, which the lungs share with other vital organs in their involvement, most of the cases belong to the tertiary period of the disease. It is a disease encountered in late middle life with an insidious and gradual onset. These cases manifest themselves with clinical findings of pneumonitis or thickened pleura, which might have been the sequelae of syphilitic pneumonias, as described by Olson and Chambers (8), or acute pulmonary syphilis described by Ornstein (9). Some tertiary cases will manifest themselves by gummata or fibrosis. These cases can never be diagnosed clinically.

The symptomatology is not typical to this disease alone, but can be found in almost any chronic pulmonary disease, particularly in tuberculosis, such as cough, expectoration, some loss of weight, frequent haemoptysis, occasionally severe pulmonary haemorrhage, dyspnoea, pain in the chest. Some will have a sense of pressure in the chest and slight limitation in breathing, associated with a cough which becomes paroxysmal after the slightest exertion. At times the cough is similar to the cough heard in bronchial asthma. The expectoration may be scanty and in some cases very profuse. With these symptoms there is usually a very slight rise of temperature in the evening hours, rapid pulse and respiration. The general appearance of the patient, whether the symptoms are slight or very marked, will never present the profound cachectic appearance such as attends advanced pulmonary tuberculosis or pulmonary malignant tumor.

Like the symptoms, there are no physical findings which are typical of this disease. There is always a limitation of the respiratory movement on the affected area. Tactile and vocal fremitus will be increased or decreased according to the type of the underlying pathological changes. Auscultation affords many interesting phenomena. Cavernous breathing may be found in some cases, and bronchovesicular breathing in others. Absence of breath-sounds and absence of tactile and vocal fremitus are found in some others. In other words there is no regularity in the physical findings of this disease. This irregularity is an especially distinctive feature of pulmonary syphilis. One thing is positive,—that the apices of the lungs appear to escape the morbid process and its signs at all times.

The roentgen-ray interpretations are interesting but not at all conclusive. Quite often the radiographic findings show dilatation of the bronchi,—a bronchiectasis. The diaphragm is higher than normal on one side. There is thickening around the bronchi and infiltration shadows as seen in bronchopneumonia. Some cases present areas of

consolidation which are prominent in the X-ray film and, depending upon the sectional views taken, mottling may also be seen. Mediastinal pathological involvement may likewise be detected at times. Perhaps the most distinctive feature of the roentgen-ray examination is the failure of the serial pictures to show progressive extension of the disease process in the presence of treatment, so pronounced in the other ulcerative affections, particularly carcinoma and tuberculosis.

The laboratory is a great aid in helping to determine the diagnosis. It is obvious that the blood examination must always show a positive serological finding, and the sputum should always be free from tubercle bacilli. Guinea-pig inoculation of sputum should be done, and, if there is a possibility, bronchoscopic aspiration of the sputum should be obtained to eliminate pulmonary tuberculosis, as often there are cases in which the two diseases cannot be differentiated. If we could demonstrate spirochetes by specific tissue stains, it would be a great help, but we do know that spirochetes are rarely demonstrated in tertiary syphilitic lesions in general; therefore it is not to be expected that the spirochetes could be found in gummata of the lungs. "At the autopsy table it is very often impossible to distinguish a gumma from a tubercle, and histologically it seems almost equally impossible to make an absolute differentiation between them. A section through a gumma in the lung tissue might have exactly the appearance of one from a large caseous encapsulated tubercle" (MacCallum (10)). The above-enumerated obstacles make the pathologist always reluctant to venture a definite diagnosis in cases of this character, rendering the roentgenologist incapable of interpreting the plates of pulmonary syphilis in a reassuring manner. Thus the clinician is compelled to assume the responsibility of the diagnosis without the support usually accorded him by the above co-workers. Hence in many cases the diagnosis is entirely speculative in character, and confusion is the result.

We readily gather that pulmonary syphilis is not only an unusual disease as to its characteristics, beguiling even the most astute investigators; and therefore many phthisiotherapists are still sceptical about its existence as a definite entity.

The tendency of spirochetes to attack vital organs has been well demonstrated, so that the assumption that the lungs may share in this involvement is by no means unreasonable. Thus we should be on the lookout for this condition at all times. But certain definite factors militate against its occurrence. Spirochetes are known to be strictly anaerobic parasites, and it is this fact that influences the infrequency of

syphilis of the respiratory tract. An excessive amount of oxygen will retard the growth of, or often destroy, the organism, which entails considerable precaution to exclude the outside air from contact with the organisms. These organisms will live in the open air without moisture but a few minutes, but with moisture may be made to live as long as eleven hours. Upon and within tissues this period may be considerably extended.

The conclusion is obvious that the spirochetes could not function in the lung very well because of the free oxygenation that occurs, unless some pathological condition had already existed, permitting the infiltration of the organisms—a hiding away, in fact, from the deterrent action of the air and its contained oxygen. This attractive explanation of the *modus operandi* of the infection by the blood-stream or the lymphatic current (a theory which I expounded several years ago) offers a great field for original work in this connection.

The differential diagnosis of syphilis of the lung is not easy. Many of the physical signs may be found in ulcerative tuberculosis, bronchiectasis, fibroid phthisis at times, and carcinoma of the lung. But the extremely slow course, the prolonged development of the symptoms and the pathological process situated mostly in the lower part of the lung should lead one to suspect syphilis. If, with this, there are positive serological findings, and prompt relief from the symptoms, together with the arrest of the extension of the radiographic findings, following intensive antisyphilitic treatment, we may then assume, with reasonable certainty, the presence of pulmonary syphilis. Sputum examination and guinea-pig inoculations in these cases should be negative. The determination of a syphilitic history and a concomitant syphilitic lesion somewhere else lend additional confirmation to the diagnosis. A study of the blood will show recuperation of the red blood cells and haemoglobin after treatment, which in other conditions are uninfluenced by treatment.

My attention has been drawn to this condition by the occurrence of one striking case of pulmonary disease, the symptoms and course of which, in my opinion, justify placing it in the class of at least suspected pulmonary syphilis.

This case occurred in

a colored male, age 38, employed in a steel-foundry, admitted to the pulmonary clinic of the Mount Sinai Hospital on May 21, 1931, with the following history: Apparently well until January, 1931, when experienced marked

night-sweats. In March, 1931, patient suddenly became faint and nauseated, and coughed up one pint of blood. No cough preceding appearance of blood, nor any difficulty in breathing. Patient immediately taken to nearby hospital, where he remained for one week, after which transferred to tuberculosis ward of another hospital where he remained three weeks. During this period he had no other attacks of bleeding. Returned to work soon after discharge from hospital, but within one week had another attack similar to the first, with loss of one pint of blood (patient's estimate). Gave no history of pain in chest; lost twenty-five pounds within four months. *Past history:* Remembers no childhood illnesses; gonorrhoea at eighteen; no history of chancre. *Family history:* Father died at age fifty; had a stroke. Mother died of heart disease. One brother died, cause unknown. Sister and brother living and well. *Physical examination:* Patient of fine physique, and well nourished. Does not appear ill. No jaundice nor cyanosis. A number of small pigmented macules over back, indicative of past dermatological lesions. Skull, scalp, eyes, and ears negative. No abnormal pulsations in neck. No lymphadenopathy. Tonsils flat and slightly reddened. Pharynx slightly injected. Teeth and mucous membranes normal. *Lungs:* Chest broad and well-formed. Left shoulder definitely lower than right. Marked lag and limitation of expansion over entire left chest, especially at base. Tactile fremitus diminished over entire left chest. Percussion note flat over entire left lower lobe and impaired over left apex posteriorly and anteriorly. Breath-sounds absent over left lower lobe and diminished over upper lobe. Vocal resonance practically absent over left lower lobe. No râles. *Heart:* Apex beat palpable and 10 cm. to left of midsternal line in 5th interspace. Supracardiac dulness 4 cm. to right, and 5.5 cm. to left. Mitral systolic and aortic systolic murmurs, with accentuation of the second aortic and second pulmonic sounds. No arrhythmia. No thrill. Pulse-rate, 80. *Abdomen:* No distention, ascites, or tenderness. Liver, spleen and kidneys not palpable. *Extremities:* Knee-jerks and biceps reflexes not elicited. Genitourinary system negative. *Rectal examination:* Prostate normal; no stricture.

On admission, patient's chest was tapped, and only 10 cc. of dark brown fluid, containing many white and red cells, were revealed. There has been no regression of his condition in the past three years. Sputum examination negative. On May 23, 1931, serological findings were strongly positive and have remained so in spite of continuous antisyphilitic treatment with iodides, bismuth, etc. On August 30, 1933, patient coughed up one pint of blood. Physical examination revealed breath-sounds in left chest absent and dulness throughout left chest. Sputum examination always negative. Spinal-fluid examination negative. Pleural-fluid aspiration showed large number of erythrocytes, fibrin, endothelial cells and small groups of polymorphonuclear leucocytes. *Roentgen-ray findings:* May 22, 1931: Right lung and diaphragm

normal. Left thorax shows extensive pleurisy, with effusion completely obscuring diaphragm and extending upward laterally in axillary line, almost to apex. Marked displacement of heart and mediastinal contents to right. The nature of any possibly underlying lung pathological changes is obscured by the pleurisy. *Roentgen-ray findings:* January 26, 1933: Thickening of right apical pleura. Otherwise, right lung presents comparatively normal appearance. Large area of increased density along external aspect of left chest, extending from first rib anteriorly to base, which we believe due to thickened pleura. This obscures left diaphragm and the greater part of left lower lobe. Left upper lobe appears to be compressed. Due to pathological changes in left chest, exact size of heart is difficult to determine: however, appears enlarged. There is aortic aneurysm, with transverse and descending portions mainly involved. *Electrocardiographic tracing report:* February 6, 1933: Cardiac rate 88. T wave upright in leads 1 and 2. No delay in AV conduction time. Ventricular complexes notched in lead 3. Left-axis deviation present. These findings, taken together, are indicative of some myocardial impairment.

In comparing the symptoms of this case and the retardation of the progress under antisyphilitic treatment, we may be pardoned for assuming a syphilitic factor in the aetiology of this pulmonary condition. It is difficult to state with accuracy the type of lesion present in this case since the anatomical characteristics of the lung make for a combination of morbid lesions no matter what may be the cause. The frank reaction of the serological examination and the equally frank response to appropriate measures indicated by the fact that the disease did not progress, the fact that the patient had concomitant lesions elsewhere, lead me to believe that we fall into no great error in regarding this case as pulmonary syphilis.

From the mass of the most confused literature concerning pulmonary syphilis, I believe it is time that this much discussed subject should have at least a working diagnosis based on clinical, laboratory and roentgen-ray findings. Obviously a pathological confirmation would strengthen the diagnosis. Having the above requirement established, pulmonary syphilis would have a much deserved chapter in our medical text books.

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GASTRIC ACIDITY IN PULMONARY TUBERCULOSIS

A Study of 50 Patients between the Ages of Twenty and Thirty Years[1]

IRVING GRAY AND JACOB MELNICK

After studying young tuberculous adults between the ages of twenty and thirty, this summary of gastric findings is being reported. These subjects had been ill with pulmonary tuberculosis from one to six years or more. They might be considered in that group, which is moderately too far-advanced and were all of the caseous-pneumonic type of phthisis, according to Ornstein's classification (1).

In a previous communication, after a study of 175 cases was made, the gastric findings in pulmonary tuberculosis were reported by one of us (2). In that study 109 men and 66 women were investigated, the ages of the patients ranging from ten to fifty years and over.

Gastric acidity and symptomatology and the presence or absence of tubercle bacilli in the gastric contents are now being reported in relation to the duration of disease.

TABLE 1

Acidity in relation to duration of disease

	0–1 YEAR	1–2 YEARS	2–4 YEARS	4–6 YEARS	6+ YEARS	TOTAL
Anacid	1	6	4		1	12
Hypoacid	4	4	4	2	1	15
Normal	1	7	7	4	3	22
Hyperacid					1	1

In the above table it is seen that 22 of the 50 patients showed normal gastric-acid values, 15 had distinct hypoacidity, 12 had anacidity, and one patient had hyperacidity. Fourteen of the 22 patients with normal acid values had pulmonary tuberculosis for from one to four years. Of these fourteen, seven or one-half had the disease longer than two years.

Friedenwald and Morrison (3) showed that, of 50 patients in the early stages of pulmonary tuberculosis, 42 per cent had hyperacidity and

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44 per cent normal acidity. We found the same percentage of normal acid values in our series. In 50 cases of far-advanced pulmonary lesions, these authors find a normal acidity in only 10 per cent, 6 per cent with hyperacidity, while 30 per cent had hypoacidity and 54 per cent showed anacidity.

Einhorn (4) reported finding hyperacidity early, although Rave (5), in a study of 30 cases in the early stages of tuberculosis, found a decrease of acidity in most of his patients.

Robin and DuPasquier (6) found hyperchlorhydria in 70 per cent of their cases in the early stages of tuberculosis and a diminution or total absence of hydrochloric acid in 75 per cent as the disease progressed.

Menzel and Schoffel (7) reported on 100 cases of pulmonary tuberculosis, mainly moderately advanced cases, with illness lasting from two months to sixteen years and found 60 per cent with hyperacidity, 24 per cent with normal acidity, 9 per cent with hypoacidity and 7 per cent with anacidity.

Faber (8), states that in one-third of all patients with pulmonary tuberculosis there is achylia.

In our study of these 50 patients, twelve, or a little less than 25 per cent, showed definite anacidity.

TABLE 2

Acidity in relation to duration of disease in 20 male patients

	0–1 YEAR	1–2 YEARS	2–4 YEARS	4–6 YEARS	6+ YEARS	TOTAL
Anacid		2	1			3
Hypoacid	1		1	1		3
Normal		5	6		2	13
Hyperacid		1				1

In the patients of table 2, some of whom had digestive disturbances, it will be found that 65 per cent had normal gastric acidity, 15 per cent had hypoacidity, 15 per cent anacidity and 5 per cent hyperacidity.

These findings might be contrasted with those of Blythe-Brook (9), who found after studying 18 cases with digestive disturbances, that 77 per cent had normal acidity and 23 per cent had hyperacidity. In a study of 21 patients without any digestive symptoms this author obtained the following results: 62 per cent with normal acidity, 10 per cent with hyperacidity, 15 per cent with hypoacidity; and in 15 per cent there was no free HCl present.

TABLE 3

Acidity in relation to duration of disease in 30 female patients

	0–1 YEAR	1–2 YEARS	2–4 YEARS	4–6 YEARS	6+ YEARS	TOTAL
Anacid	1	4	3		1	9
Hypoacid	4	3	3	1	1	12
Normal	1	2	1	4	1	9
Hyperacid						

The figures in table 3, taken from the findings on female patients that fall into the same group as the male patients mentioned in table 2, show 30 per cent with anacidity, 40 per cent with hypoacidity, and 30 per cent with normal acidity. This seems to coincide with the experience of Vanzant (10), who states that "At all times women appear to be slightly more subject to achlorhydria than are men."

TABLE 4

Tubercle bacilli in the gastric contents in patients with positive sputum in relation to duration of disease

	0–1 YEAR	1–2 YEARS	2–4 YEARS	4–6 YEARS	6+ YEARS	TOTAL
Tubercle bacilli in stomach contents	5	11	8	3	4	31
No tubercle bacilli in stomach contents	1	7	7	3	1	19

In this group of 50 patients, eight had negative sputum and in these eight no tubercle bacilli were found in the gastric contents. The examination of the gastric contents for tubercle bacilli was made in association with test-meal studies. At present, gastric lavage is being done before breakfast, and, in a few patients with negative sputum, tubercle bacilli have been found in the gastric washings. These cases are not included in this study. The finding of tubercle bacilli in the gastric contents when the sputum is negative has been reported by several observers. In children who cannot and do not expectorate this method of searching for the tubercle bacillus is undoubtedly the method of choice.

Recently Kereszturi (11) and her co-workers reported such findings after studying a group of children.

Friedenwald and Morrison (3) state that tubercle bacilli are often found in the fasting contents in early stages of the disease, often before physical signs of the disease are evident.

In the 42 patients with positive sputum, the microörganism was found in the gastric contents of thirty-one. It is reasonable to assume that with

more frequent study the tubercle bacillus would probably have been recovered in all subjects.

TABLE 5

Relation between tubercle bacilli in stomach contents and acidity

	ANACID	HYPO-ACID	NOR-MAL	HYPER-ACIDITY	TOTAL
Tubercle bacilli in stomach contents	10	9	11	1	31
No tubercle bacilli in stomach contents	1	3	7		11

In table 5 it will be noted that the tubercle bacillus was found in the gastric contents most frequently in the anacid and hypoacid groups. A little more than one-half the patients with normal gastric acidity had tubercle bacilli in the gastric contents. Seven of the 11 patients who had no tubercle bacilli in the gastric contents had normal gastric acidity. It is evident that in patients with high acid values tubercle bacilli are found less frequently in the gastric contents than in those who have a decrease or absence of HCl. This, however, is not due to the bactericidal power of the gastric secretions, as has been shown by numerous investigators. Inkster and Gloyne (12) have demonstrated that gastric secretion will not destroy tubercle bacilli in the sputum even after ninety minutes' exposure.

Straus and Wurtz (13) found that the tubercle bacillus will not lose its virulence after six hours exposure to the gastric juice.

Frank (14), as early as 1884, concluded that the gastric juice does not inhibit the action of pathogenic bacteria to any marked degree.

TABLE 6

Relationship of the gastrointestinal symptoms in males to acidity

	ANACID-ITY	HYPOACID	NORMAL	HYPER-ACID	TOTAL
Presence of symptoms	2	2	5	1	10
Absence of symptoms	1	1	8		10

TABLE 7

Relationship of gastrointestinal symptoms in females to acidity

	ANACID	HYPOACID	NORMAL	HYPER-ACID	TOTAL
Presence of symptoms	8	5	4		17
Absence of symptoms	1	7	5		13

From tables 6 and 7 it will be noted that 50 per cent of the males and 57 per cent of the females had gastrointestinal symptoms. Although these figures are by no means conclusive, they tend to bear out the findings of others that in tuberculosis gastrointestinal symptoms are more common in the female than in the male.

Fishberg (15) stated that 17 per cent of the males and 72 per cent of the females studied had dyspepsia as the first symptom of pulmonary tuberculosis.

Digestive symptoms were more common when anacidity or hypoacidity were found to be present. Complications were present in 80 per cent of the anacid group, 56 per cent of the hypoacid group and 40 per cent of the normal acid group.

Henning, Schatzke and Ornstein (16) in 39 cases of pulmonary tuberculosis found 44 per cent with digestive symptoms and 70 per cent of the patients with gastrointestinal symptoms showing anacidity.

TABLE 8

Gastrointestinal symptoms in males in relationship to duration of disease

	DURATION					TOTAL
	0–1 year	1–2 years	2–4 years	4–6 years	6+ years	
Presence of symptoms.....		6	2	1	1	10
Absence of symptoms.....	1	2	6		1	10

TABLE 9

Gastrointestinal symptoms in females in relationship to duration of disease

	DURATION					TOTAL
	0–1 year	1–2 years	2–4 years	4–6 years	6+ years	
Presence of symptoms.....	4	6	4	2	1	17
Absence of symptoms.....	2	3	3	3	2	13

From a review of tables 8 and 9, there appears to be no relation between the duration of the disease and the gastrointestinal manifestations. It seems that, as the duration of disease progressed, the gastrointestinal manifestations decreased. Clinically, however, we know that such is not the case. These tables agree with our clinical experience in that most of the abdominal symptoms are present within the first three or four years of pulmonary activity. It will be noted that, of the 17 patients who presented symptoms, practically all had complaints during the first four years.

The absence of symptoms, in this group, after the disease had existed for six years and the acute phase had subsided, may depend on many factors.

SUMMARY

1. In young individuals pulmonary tuberculosis produces gastric hypoacidity in approximately one-third and anacidity in one-fourth of the patients within a period of one to four years. Approximately one-half the number show a normal acidity at all times.

2. In male patients a little more than half show normal acidity through a six-year period of disease. Approximately one-third show a decrease or absence of acid.

3. In the female normal acidity is present only in one-third of the patients with a decrease or absence of acid values in the other two-thirds. There is a definite tendency in the female toward a decrease in acid values.

4. The gastric contents show tubercle bacilli in the majority of these young adults. As the acid figures decrease tubercle bacilli are found more frequently in the stomach contents.

5. Gastric symptoms are somewhat more frequent in the female than in the male, and usually start at an earlier period.

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SUBSURFACE GROWTHS OF MYCOBACTERIUM TUBERCULOSIS IN SOLID CULTURE MEDIA[1]

J. M. THURINGER AND H. W. BUTLER

A review of recent literature indicates marked changes in the morphological concept of the tubercle bacillus. Briefly, the early phases of these researches deal with the recording of unusual forms of bacilli, long slender threads, branched forms, coccoid forms, etc. Next, the variability in acid-fastness of these forms and its possible relationship to increased or diminished virulence received attention. The question of the existence of filterable viruses was studied chiefly by the French school of investigators.

These observations, quite reasonably, lead to the conclusions that tubercle bacilli may be encountered in various phases and the many forms observed merely represent stages of a cycle in the life of the organism.

In 1929 Kahn (1) succeeded in separating individual organisms by means of the Chambers micromanipulator and observing their development in micro-drop cultures. He used a strain of human tubercle bacilli designated as H37 and "a wild strain isolated from sputum which gave identical results." From his observations he concluded that the tubercle bacillus does not reproduce by simple fission but undergoes a more complex type of reproduction which may be briefly summarized as follows:

1: Initial segmenting of the rod into three or more ovoid units;
2: The division of these units into diplococcoid forms;
3: The subsequent grouping and reduction of these elements to a mass of dust-fine particles from which extremely small and delicate rods were found to sprout;
4: The later development of these tiny rods into mature tubercle bacilli.

This work was recently subjected to a rather critical polemic by Oerskov (2), who investigated about 80 strains of mammalian tubercle

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bacilli, principally human, and came to the conclusion that "there exists at present no basis for the necessity of a thorough revision of the classical concept of the morphology of the tubercle bacillus, especially not in the direction suggested by Kahn."

Mellon (3) and others reported a definite life-cycle of the avian tubercle bacillus consisting of four stabilized stages which are vegetative and three transition stages between them which are reproductive or gonidial. The possibility of a sexual stage is mentioned and evidence of the existence of nuclear structures presented by Lindegren (4) and others.

Kahn (5) recently reported the presence of three distinctly stratified zones in vertical sections through a surface colony of human tubercle bacillus culture. This stratification was due to the relatively different rate of growth and the peculiar arrangement of acid-fast and non-acid-fast rods and granules.

With this rather sketchy introduction we desire to present our observations made during the past year. When this work was undertaken, the recent papers of Mellon and Kahn had not appeared in print and we concerned ourselves with the task of attempting to establish an orderly relationship of the organisms to the medium upon which they grew, realizing that in the customary smears all possible previous relationships of organisms toward one another, if any such existed, must be destroyed.

Observations on subsurface growths of tubercle bacilli in liquid media and gelatine have been made by other investigators. These, however, have been described as growth clouds and interpreted as being aggregations of old and disintegrating organisms.

For a number of years we have been cognizant of the fact that, in cultures of tubercle bacilli on certain solid transparent media, there was present a peculiar cloudiness just below the surface growth. Occasionally a thin veil-like structure could be seen to penetrate from the surface growth into the substratum for a considerable distance. We decided to make use of histological methods for the preservation of the relationship of these subsurface growths and to keep intact the relationship of colony to media.

MATERIALS AND METHODS

The strains of the tubercle bacilli studied originated from the following sources: (1) New York State Board of Health, H54; (2) Department of Bacteriology, University of Oklahoma; and (3) Fitzsimons General Hospital, Denver, Colorado.

The early growth of the organisms was studied on small agar-block cultures. Cultures were also grown in specially made thin glass cells, between cover-glasses and in hanging drops. These, however, did not give us the desired information since we were particularly interested in the study of the substratum. We then resorted to the use of the common culture-tube slants, using Corper's and Petroff's media, glycerine-potato, glycerine-agar, Russell's double sugar, dextrose-agar, blood-agar, liver-agar, testis-agar and litmus-lactose.

All three strains of the organisms were used in the beginning; however, since they showed no appreciable difference in their behavior, we decided to use the H54 strain exclusively.

The routine paraffine technique combined with carbolfuchsin staining presented too many objectionable features, such as destruction of the finer clusters of organisms on removal of the paraffine and the annoying deposits of stain obscuring detail. A modified celloidin technique and aniline-fuchsin-Gabbet stain were developed, and were found to give uniformly good results.[2] The acid-fastness was checked in every instance against the standard Ziehl-Neelsen method. Vertical sections were made of cultures on all the media mentioned above except Corper's, Petroff's and glycerine-potato.

OBSERVATIONS

To elucidate the meaning of surface and subsurface growth two photomicrographs of *Staphylococcus aureus* and *B. diphtheriae* are submitted (figures 1 & 2), which show clearly that these organisms are strictly surface-growers. The surface of the underlying media presents an unbroken line.

Blood-agar: Growth very wrinkled, surface growth most pronounced. A stratification of the surface layer into three zones was occasionally present when the surface growth began to elevate itself from the medium but, where the surface growth was in contact with the medium and extended into it, no such stratification was noticed. Vacuolization of the outer zone was the rule.

The subsurface growth was irregular and scanty. The acid-fast rods were of extreme delicacy and branched profusely.

Russell's double agar: Surface growth slightly wrinkled and of almost uniform thickness, with many vacuoles (figure 3). No definite stratifica-

[2] Method to be published elsewhere.

tion of the surface growth could be seen. It was largely composed of non-acid-fast rods and granules with acid-fast rods unequally scattered throughout.

Subsurface growth was present, paralleling almost the entire surface growth. The extent of the subsurface growth into the medium was greater in depth than the thickness of the surface growth. In a few instances there was only an occasional cluster of rods present in the substratum covered by a rather thick surface growth, while in other places, in the same section, clusters were present in the substratum without any surface growth over them. The clusters of organisms in the subsurface growth contained more acid-fast rods than the surface growth, although, here too, the non-acid-fast variety predominated. A few clusters, composed almost exclusively of acid-fast rods, were present.

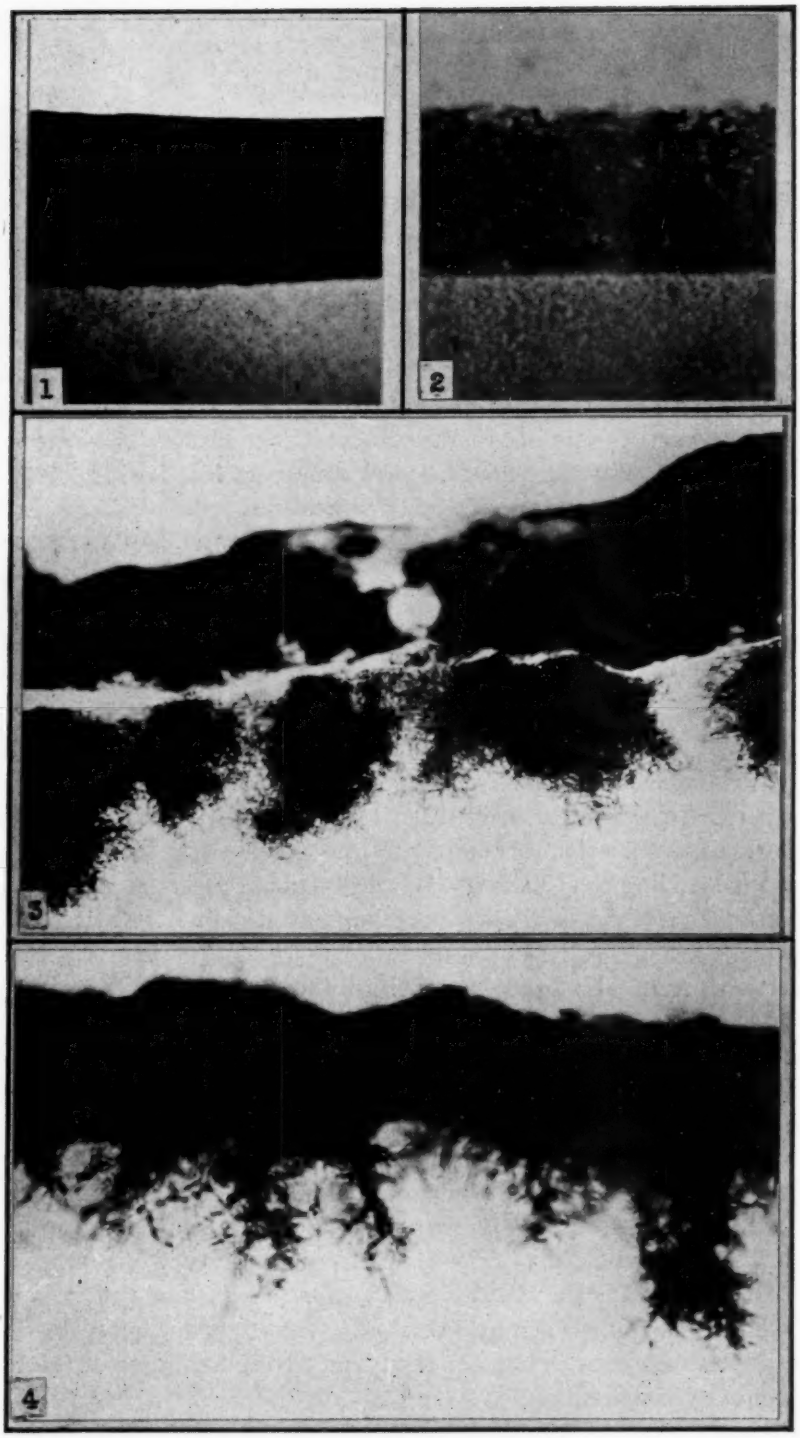
Litmus-lactose: Surface growth very thin (figure 4). Nodular masses were present at irregular intervals. These consisted of very dense aggregations of granules and partly acid-fast rods. The apices of the nodules pointed toward the substratum where they terminated in compact masses extending into the medium. On the upper surface of the nodules just mentioned only very small coccoid forms were seen.

Subsurface growth was composed of a fairly dense mass of branched rods of variable acid-fastness. A superficial glance at this growth would lead one to believe in the presence of many acid-fast granules; however, upon closer examination it is noted that the granules are merely branches of rods seen in vertical plane. The thickness of the subsurface growth was approximately equal in depth to the greatest diameter of the surface growth.

Sections were also made parallel to the surface of litmus-lactose cultures, near the edge of the growth (figure 5). The pictures obtained looked like the early growths of the organisms previously observed on the surface of the small agar block cultures.

Testis-agar: Surface growth was abundant and uniform in thickness, but extremely wrinkled and without stratification, practically non-adherent to the medium. Very small cocci were visible on the upper surface. There were also present peculiar, thick, conical projections with blunt terminations. These appeared to consist of compactly arranged rods. In other localities they were seen to give rise to skeins.

The rods of the surface growth were extremely short, non-acid-fast, the granules ranged in diameter from that of the thickness of the rods to the limits of visibility.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The subsurface growth on testis-agar was extremely meagre, penetrating the surface but slightly. Only a few clusters of non-acid-fast rods were encountered.

Liver-agar: Surface growth was very uneven and of crumbly consistency, composed almost entirely of non-acid-fast rods and granules, very compact. Short conical projections, similar to those described above, were frequently seen to arise from the apices of the granular masses. The granules ultimately formed vesicles which sometimes lost their continuity with the surface growth (6). They consisted of an outer, more or less compact mass of non-acid-fast granules and rods, with a thinner lining of granules almost exclusively. Only a few scattered acid-fast rods were found in the entire surface growth.

The subsurface growth while not very abundant, frequently was observed to consist of rather large clusters of branched rods, the terminal ones usually being acid-fast (figure 7).

Dextrose-agar: Surface growth on this medium was extremely irregular in thickness with quite a few surface granulations. An occasional granule showed a distinct stratification into three zones (figure 8) A, B, C, the inner zone consisting of definitely mature, acid-fast rods, extending down into the medium wherever in contact, forming clusters of acid-fast branching rods as shown in the lower left corner of the photomicrograph. The remainder of the surface growth, in contact with the medium, did not show any stratification.

The subsurface growth, while quite uniform in its relationship to the surface growth, was very thin and extended into the medium only about one-half the thickness of the surface growth. The rods were extremely slender, long, branched, and acid-fast.

Glycerine-agar: Surface growth irregularly thick and closely adherent to the medium (figure 9). Stratification, such as was observed in blood-agar and dextrose-agar, was not present anywhere. The growth was very compact, consisting of rods and granules.

Fig. 1. Vertical section through culture of *Staphylococcus aureus* on plain agar medium. Growth strictly confined to the surface of the medium. Photomicrograph, × 400.

Fig. 2. Vertical section through culture of *B. diphtheriae* on Loeffler's blood-serum. Strictly a surface growth Photomicrograph, × 400.

Fig. 3. Vertical section through culture of *M. tuberculosis* on Russell's double-sugar medium, showing relationship of surface to subsurface growth; vacuolization and thinning of surface growth; "bushy" subsurface growth. Photomicrograph, × 400.

Fig. 4. Vertical section through culture of *M. tuberculosis* on litmus-lactose, showing a very strong subsurface growth. Photomicrograph, × 400.

Subsurface growth consisted of numerous "moss-like" downgrowths, composed of short branched rods of variable acid-fastness, the longer forms reaching as far into the medium as the diameter of the surface growth. In several localities, however, a decided departure from the above recorded observations was noticed.

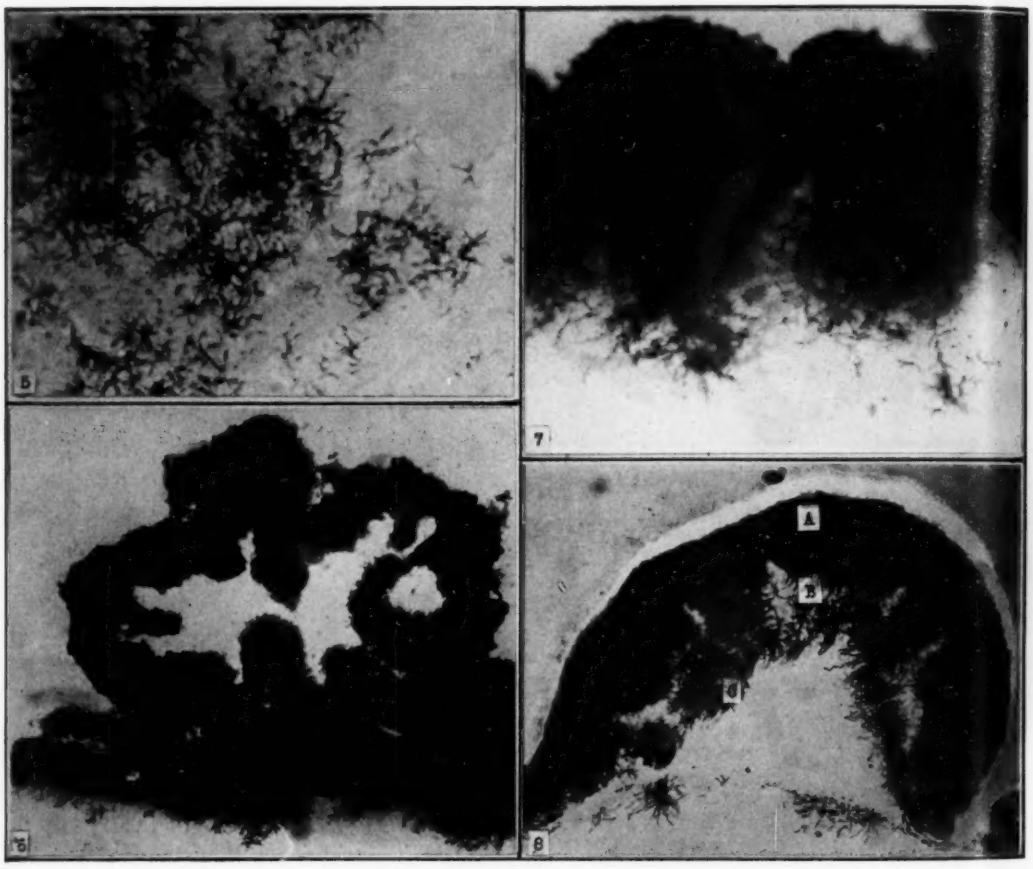

Fig. 5. Same culture as fig. 4. Section parallel to surface near edge of growth, showing the subsurface growth on a horizontal plane. Photomicrograph, × 534.

Fig. 6. Vertical section through a surface granule, surface and subsurface growth on liver-agar. Photomicrograph, × 266.

Fig. 7. Vertical section through same culture as fig. 6, showing detail of subsurface growth. Note the branching in the lower right corner. Photomicrograph, × 534.

Fig. 8. Vertical section through culture on dextrose-agar, showing a portion of the surface growth elevated in process of forming a surface granule. Stratification into three zones A, B, C, is distinct. In the lower left corner the acid-fast rods of the inner zone are embedded in the medium. Photomicrograph, × 266.

In practically all cultures on this medium and in some on dextrose-agar, we were able to obtain quite an extensive localized downgrowth, which upon very close inspection with the unaided eye appeared as a delicate veil-like structure. This downgrowth had a peculiar mossy appearance, and consisted of short, branching acid-fast rods (figure 10).

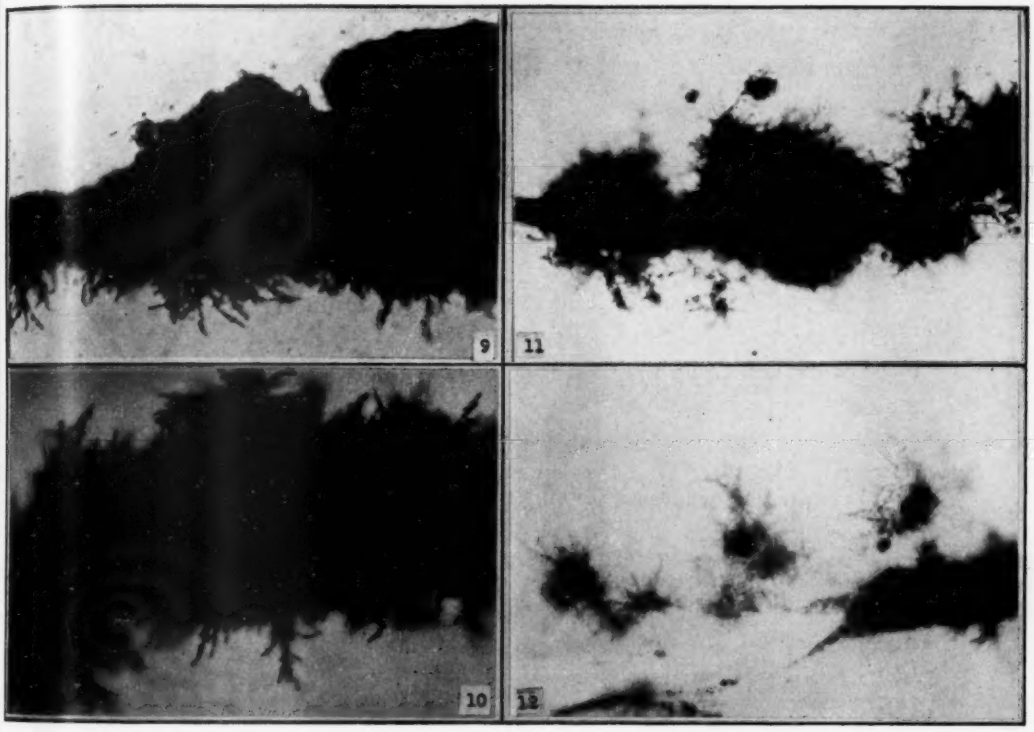

Fig. 9. Vertical section through culture on glycerine-agar, showing dense surface growth of irregular diameter and subsurface growth of short, branching, acid-fast rods. Photomicrograph, × 400.

Fig. 10. Longitudinal section through veil-like downgrowth from the same culture shown in fig. 9. The "moss-like" appearance of the whole growth as well as the branching is clearly shown. Photomicrograph, × 534.

Fig. 11. Longitudinal section of another portion of the same culture as fig. 10. The clumps of organisms appear more dense. From the periphery of the clusters small buds appear, suspended on delicate stalks of acid-fast rods. The buds are composed of granules of extremely small size. A few slender branches may be observed to issue from the stem of the bud A as well as from the granular mass of the bud itself. Portions of other buds, cut in sectioning, may also be seen. Photomicrograph, × 400.

Fig. 12. Section through the same culture as fig. 10. A small cleft is visible in the medium. From the masses of dust-fine particles, new branched rods appear forming the clusters. Photomicrograph, × 400.

Following the growth further down into the medium, the clusters took on a more compact appearance (figure 11). From their periphery, bud-like processes supported on delicate branching stems were seen. The stems were made up of acid-fast rods while the buds consisted of very minute granules. From the periphery of the buds extremely slender, branched rods again projected.

The progress in the development of these buds is shown in figure 12, which is from another portion of the same glycerine-agar culture. The central granular mass is still present while the rods growing from the surface have given rise to new clusters.

SUMMARY

A subsurface growth of the *Mycobacterium tuberculosis* on various solid media has been shown to be a more or less constant phenomenon.

Further evidence is presented that this organism is capable of responding to its environment in many different ways. (Depending upon conditions of oxygen concentration, reaction of media, temperature, moisture and its own metabolic products.)

We are in agreement with those who believe that this organism occurs in various forms and that these pass through a cycle consisting of several phases, but we are unable to demonstrate the factors which bring about these changes.

It is of interest to note that most of the acid-fast rods were found in the subsurface growths, their profusion, arrangement, and acid-fastness depending upon the medium used. This may well lead to the question, "whether this subsurface growth does not resemble the actual status of this organism growing in the tissues more closely than the surface growth."

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THE ALTERNATELY EXPANDING AND CONTRACTING TUBERCULOUS CAVITY[1]

EPHRAIM KOROL[2]

Several observers have written about cavities which closed suddenly only to reappear in the same part of the lung. Various explanations have been offered for this phenomenon. Reinders (1) states that the volume of the cavity does not represent the amount of lung tissue actually destroyed, but largely lung which has collapsed and which is still capable of expansion. A slit in a tense elastic membrane becomes a circular hole; stretching the membrane enlarges the hole much more than the membrane. In an actual experiment the membrane stretched to 2.34 times its original area, while the hole enlarged 9 times. This may be a reason for the rapid formation and closure of cavities, but does not explain why certain cavities periodically open and close.

Bronkhorst (2) calls attention to the elasticity of the lung distal to the cavity. If the lung is fairly healthy the cavity may close readily (due to some unknown factors) and the healthy lung will expand to obliterate the cavity. Conversely, rapid infiltration and contraction of the surrounding lung will tend to stretch the cavity. But how to explain the sudden reopening of a cavity without other demonstrable changes in the surrounding lung?

Alexander (3) states that the annular shadow signalizing a cavity on the X-ray films does not actually represent the extent of the excavated lung but merely a line of demarcation inside of which good lung tissue still remains. Alexander says it explains the appearance, disappearance and reappearance of annular shadows at the same place. But why should certain annular shadows show such fluctuation in size while the great majority of these shadows are very slow in their progression as well as in their retrogression?

It occurs to me that the condition of the draining bronchus has a deter-

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[2] Veterans' Administration, Lincoln, Nebraska.

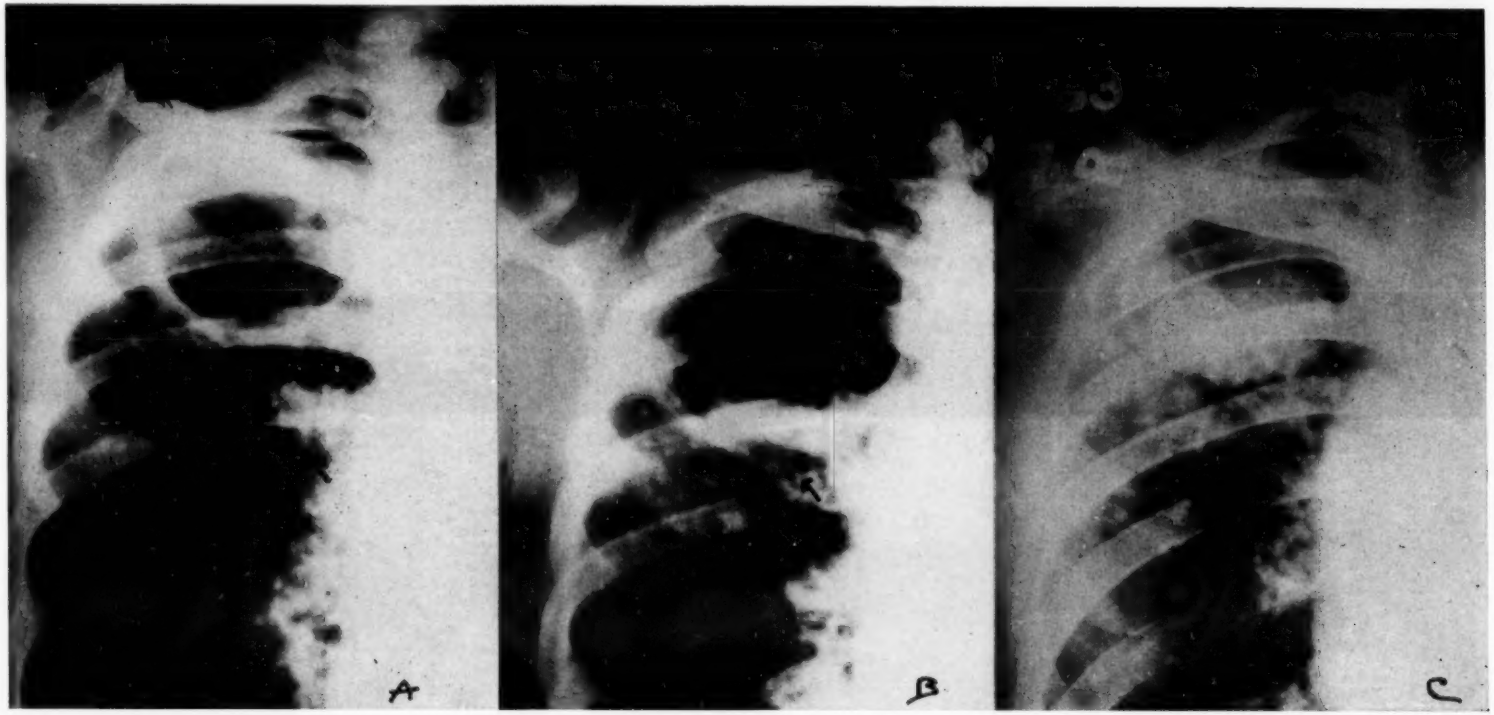

FIG. A. May 4, 1933. Large cavity in upper lobe, lower border in 2nd interspace anteriorly; through the lower part of the cavity normal lung markings can be seen. The arrow points at the upper-lobe bronchus which shows in "cross-section."

FIG. B. May 19, 1933. The cavity enlarged in all directions. The lower border is in the 3rd interspace; the neighboring lung seems compressed. Lung markings no longer seen through the cavity. The latter has encroached on the mediastinal shadow and on the rib shadows in the axilla, causing the 2nd and 3rd ribs to bulge outward. We believe the pressure in the cavity to be above atmospheric. There is a blood-clot in the cavity and in the lumen of the bronchus.

FIG. C. The bronchial lumen is patent. The cavity has contracted in all directions.

mining influence on the size and progress of the cavity. A temporary narrowing of the bronchus will lead to sudden enlargement of the cavity; a return of the lumen to its former size will result in rapid shrinking of the cavity.

PHYSIOLOGICAL CONSIDERATIONS

The bronchi enlarge and widen in inspiration and contract in expiration; this accounts for the residual air normally present in the lungs. In labored breathing, as during physical effort and after fits of coughing, the contractions of the bronchi are exaggerated and there is a rapid accumulation of residual air (*volumen pulmonum acutum*). The narrower the bronchus the more tendency to residual air; hence the acute emphysema in bronchial spasm (asthma). People with long narrow bronchi are predisposed to the development of emphysema (4). Narrowing of a bronchus by a stricture leads to overinflation of the supplied lobule: during inspiration the bronchus relaxes to admit some air; during expiration the bronchus collapses about the strictures, and the air is entrapped: there results an obstructive emphysema (5). The bronchi supplying tuberculous cavities are not infrequently constricted or tortuous, as can be observed on X-ray films. During expiration these cavities brighten up fluoroscopically,—the surrounding lung collapses, but no air can escape from the cavity due to expiratory occlusion of the bronchial lumen about the stricture.

Morin and Waitz (6) described a case in which the cavity opened and closed repeatedly seven different times. Fluoroscopically they observed that the cavity illuminated during expiration. They did not, however, correlate this phenomenon with the fluctuating size of the cavity, nor with the condition of the bronchus. Elsewhere (7) we have presented illustrations of tuberculous cavities enlarging in expiration. It is well known that emphysematous vesicles enlarge during expiration and during manual compression of the lung on the autopsy table; this expiratory enlargement is caused by the underlying bronchial stricture; indeed the repeated expiratory efforts of coughing and of physical labor gradually produce these blebs in the presence of strictures. It is believed that many tuberculous cavities have a similar origin, that is, after a stricture develops in the draining bronchus, cavitation proceeds rapidly. The air in such cavities is likely to be under pressure above atmospheric (8), (9). The cavities have a spherical shape in life; that is, on X-ray examination, but upon postmortem opening of the cavity the shape is

anything but spherical. It is on account of these strictures that it is difficult to inject lipiodol into such cavities and into emphysematous vesicles (10) (11) (12).

The narrowing of the draining bronchus may be temporary, due to catarrhal swelling, granulation tissue, foreign-body, caseous material, tenacious sputum, or to a blood-clot. Cavities have thus been seen to reopen or to enlarge following a head-cold or an attack of grippe (13) (14). After the bronchial passage has returned to normal the cavity shrinks rapidly.

Case Report

Colored male, aged 37, admitted June 27, 1932, following a pulmonary haemorrhage. In October, 1932, during an haemoptysis, pneumothorax was induced on the right side; this was later discontinued on account of extensive adhesions. In November the right diaphragm was paralyzed in order to control a haemorrhage. In May, 1933, there began a series of small haemorrhages. The blood-clots were unusually firm and collected in large hemispherical masses like gobs of jello.

At 1:15 P.M., July 19, the man was unable to expectorate. He was restless, tossing about in bed. Breathing was labored, the abdomen and neck were drawn in with each inspiration, but no breath-sounds were heard over the chest (tracheal obstruction). The man got out of bed, he was helped to the window, he turned towards the electric fan, he lay back in bed, and presently went into a convulsion. It was a clonic spasm chiefly affecting the head and face; the eyes rolled to the right. Chest movements ceased and the pulse became feeble. The patient was placed across the bed, face down, head and shoulders suspended, and artificial respiration was employed. A branching blood-clot, eight inches long and ½ inch wide, was dislodged from the throat. Automatic respiration soon returned. There was some retching and vomiting of blood. The man regained consciousness, he was very talkative, but was unable to see for some ten minutes.

There followed an aspiration pneumonia and the patient died on August 1, 1933.

All X-ray films of the chest showed the upper-lobe bronchus plainly. On May 19 the film showed a clot nearly occluding the lumen of the bronchus, while the cavity in the right upper lobe, also containing blood, was much larger than on the film taken two weeks previously. On May 27 the film showed the bronchial lumen patent and the cavity much reduced in size.

In brief: In a case of haemoptoic tuberculosis there was difficulty in expectorating. A blood-clot partly occluded the upper-lobe bronchus and caused an enlargement of the cavity in the upper lobe. The extrusion of the clot resulted in a contraction of the cavity.

SUMMARY AND CONCLUSIONS

The cause of sudden changes in the size of a tuberculous cavity is to be looked for in the state of the draining bronchus. A temporary narrowing of the bronchial channel, as by a blood-clot, catarrhal swelling, caseous material, etc., may cause a ball-valve mechanism with expiratory obstruction and rapid enlargement of the cavity. Relief of the obstruction leads to contraction of the cavity.

A case is described in which the right upper-lobe bronchus was partly occluded by a blood-clot which was visualized on the X-ray film. There resulted an enlargement of the cavity in the right upper lobe. After the discharge of the clot the cavity promptly returned to its original size.

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THE VALUE OF THE LEUCOCYTIC PICTURE IN THE MANAGEMENT OF TUBERCULOSIS[1]

JACOB KAMINSKY

In studies on the blood picture in tuberculosis, three cell types have been found to be of special significance: the monocyte, the lymphocyte, and the polymorphonuclear leucocyte. The rôle of the monocyte in tuberculosis was studied by Sabin, Cunningham and Doan (1). They described observations which indicate that the epithelioid cells of the tubercle are derived from the monocyte. Cunningham, Sabin, Sugiyama and Kindwall (2) made further observations on the rôle of the monocyte in experimental tuberculosis. They found that the course of the disease in experimental tuberculosis may be quite accurately followed by observing the relative proportion of monocytes and lymphocytes in the peripheral blood. They found that when animals were killed at a time when the monocytes were markedly increased in the peripheral blood, autopsy showed most extensive and active disease. On the other hand, when lymphocytes in the peripheral blood were much more numerous than the monocytes, the disease was not widespread or it was arrested. These observations led to the introduction of the idea that the monocyte-lymphocyte ratio could be used as an index of the condition of the tuberculous animal. Cunningham and Tompkins (3) in their observation on the leucocyte count in human tuberculosis found the monocyte-lymphocyte ratio a useful mathematical expression for the extent of invasion as compared with that of resistance. They state that the ratio is practically always elevated (above 0.3) in tuberculosis and parallels increased clinical severity. The above investigators did not attach much significance to the polymorphonuclear leucocyte in the blood picture in tuberculosis.

Medlar and Kastlin (4), on the other hand, include in their interpretation of the blood picture in tuberculosis all of the three cell types. They lay much stress on the neutrophile, this being the cell chiefly concerned in tuberculous abscess-formation. They state that the greater the deviation of the neutrophiles from the normal, the worse the prognosis.

[1] From the Middlesex County Sanatorium, Waltham, Massachusetts.

An increase in mononuclears may mean, according to these investigators, either new tubercle-formation or repair of a caseated lesion. An increase in lymphocytes signifies a tendency to repair. A simultaneous or closely related increase of neutrophiles and mononuclears is an indication of spread of infection and formation of new tubercles which go on to abscess-formation. An increase of lymphocytes and of mononuclears with little or no increase of neutrophiles indicates good repair with little or no abscess-formation.

In another publication (5) Medlar described a mode for the normal leucocytic formula: Total count 6,000 to 9,000 cells per cmm.; upper limit of normal for polymorphonuclear leucocytes, 5,000 cells per cmm. of blood; upper limit of normal for mononuclears, 700 cells per cmm.; and lower limit of normal for lymphocytes, 2,000 cells per cmm. of blood.

Many others have studied the white blood cells in tuberculosis. As yet, however, the test has not gained wide acceptance. The extent to which it can be utilized in judging activity and prognosis is still a debatable question. Some observers claim that the leucocytic picture is the best single means of judging activity in this disease, while others find that it can add little to what may be learned by our other well-established methods. Needless to say that to the clinician this controversy is of more than academic interest, for it must be admitted that situations are often met with when additional data, even of corroborative nature, are of inestimable value. If the leucocytic picture could furnish such data, it deserves the esteem in which it is held by its staunch advocates. Further clinical reports should aid in clarifying this point.

METHOD AND OBSERVATIONS

This report is based on a study of 1,100 total and differential leucocyte counts on an unselected group of 117 patients with pulmonary tuberculosis under treatment at the Middlesex County Sanatorium. This group consisted of 73 women and 44 men. Their ages ranged between 17 and 56. All stages of the disease were represented and some of the patients also had extrapulmonary complications.

In 71 cases only one to several counts were done; in the remaining 46 cases, counts were repeated at frequent intervals (every 2 to 3 weeks during the greater part of the period of observation in each case). Of the 46 cases, 16 were observed for periods ranging from 4 to 11 months, and 30 from 12 to 17 months.

Uniformity of technique was stressed by all who used this test. The state of patient, especially with regard to exercise and posture, before and while the count is taken, is one phase of the technique which has hitherto received little consideration. The importance of the physiological state of the subject during and before the count is taken was strikingly brought out in recent investigations by Garrey and Butler (6) (7) (8) (9). These authors have noted that exercise, change of posture, bodily discomfort, fright or apprehension, tend to increase the leucocytic count in subjects whose counts were previously at a lower level. They found that the leucocyte count falls and reaches its lowest level within an hour with the subject at absolute rest in a recumbent position. This low level they designate "basal level," and for most human individuals it lies between 5,000 and 6,000 cells per cmm. of blood. When the subject changes his posture, the count rises, and its level will depend on the amount of activity. For most individuals pursuing the ordinary routine of a medical school laboratory, the leucocyte counts averaged around 9,000. This, they designated "activity level." They noted that severe physical effort may raise the count to very high levels. Values as high as 20,000 to 35,000 were obtained in athletic competition. The rise in the leucocytes following alteration in the physiological state of the individual is attributed by these investigators to vasomotor changes which result in the liberation of leucocytes trapped in unused capillaries.

During the early part of this study, the author was unaware of the findings of the above investigators, but since June, 1932, all counts were done under basic conditions. It was also thought that it might be of interest to repeat some of the observations of Garrey and Butler on tuberculous subjects. This was done on a group of 50 patients and the differences between the leucocyte counts done under basic conditions and those taken after some exercise were very marked in some instances. The findings have been reported in detail in a previous publication (10).

It might be pointed out here that the morning hours between 8 and 10 in most sanatoria are particularly unsuitable for taking counts if no precautions are exercised to keep the patient at rest. Ordinarily after breakfast, beds are made, wards are brought into order, patients are moving about more or less and do not settle down to rest for some time. The counts may, therefore, show deviations due to exercise or nervous strain.

Under our modified technique, the patient was required to stay in bed

at rest and relaxed for at least one hour before the count was taken (all counts were done between 9 and 10 A.M., thus giving the patient sufficient time to rest after breakfast which was usually served between 7 and 8 A.M.). The patient was not allowed to read, listen to the radio or engage in conversation during the hour preceding the test. The object of the test was explained to the patient and every effort was made to gain his full coöperation.

In all instances, blood was taken from the finger. Smears were made on no. 1 cover-slips and stained with Wright's stain. Certified pipettes and counting-chambers were used and 4 large squares were taken for the total counts. In the differential counts 200 cells were counted. The cells were grouped into polymorphonuclear leucocytes, lymphocytes (large and small), monocytes, eosinophiles and basophiles. (The author has done all of the differential counts and the total counts were done by a trained technician.)

Medlar's concept of the leucocytic picture, which includes the polymorphonuclear leucocyte as well as the monocyte and lymphocyte, was followed in evaluating the results of this study. The polymorphonuclear leucocyte was found to be the chief cell concerned in abscess-formation in tuberculosis. A formula which includes this type of cell seems to be best adapted to the study of the blood in human pulmonary tuberculosis, in which we are dealing with an allergic host and the tuberculous process consists of nodular formations as well as exudative reactions of varying degrees with resulting abscess-formation.

Throughout this study an answer was sought to the following question: Does the leucocytic picture furnish data which would help the practitioner in tuberculosis in the management of his patient? That a study of the white blood cells in tuberculosis comprises in itself a rather interesting bit of clinical investigation is conceded by all. The clinician, who undertakes to do the work himself, may even feel well repaid for his efforts, for it is indeed refreshing to divert for a moment from viewing the shadows of the lesion as seen on the roentgenogram and have a glimpse at the actual components, the brick and mortar, so to speak, which enter into the formation of the lesion. But, however interesting this investigation may be, does the information gained warrant more expense to the patient or added personnel to a sanatorium laboratory? Could the leucocytic picture help solve some of our difficult problems in prognosis? When to increase a patient's activities is at times a difficult matter to be decided. We are all familiar with the instances in

which we had to retrace our foot-steps and return the patient to bed. Again, with the great advances made in recent years in the treatment of tuberculosis, the phthisiotherapist became liable to sins of commission as well as of omission. He has to determine when collapse therapy is indicated, and his opinion is sought by the surgeon as to when major surgery on the chest is to be performed. Could we gain any aid through the study of the blood in such problems?

In the series of cases under observation, no attempt was made to utilize the blood findings as a guide in treatment. Instead, the series of blood pictures in each case was analyzed after the completion of this project with a view to determine the possibilities it offers in the management of the tuberculous patient.

In many instances, it was found that a judicious application of the information gained from the blood picture could have been utilized to great advantage.

The leucocytic picture, in the words of Medlar, is our nearest approach to the lesion in the living body. The blood picture reveals information as to the status of the lesion which cannot be obtained by any of our other well-established methods of study. It was found in this study that a blood picture in which the polymorphonuclears are high and the monocytes and lymphocytes very low is a bad prognostic sign. On the other hand, blood pictures with polymorphonuclear leucocyte counts equally high, but with moderate elevation of monocytes and tendency of the lymphocytes to rise frequently above 2,000, indicate a more hopeful outlook. Patients showing this type of blood picture have been seen to improve. Our observations here failed to corroborate the findings of other investigators who stated that cases even with the worst type of blood may improve. The contrary was noted. Patients with good blood pictures have later developed exacerbations of their lesions. Those who had the worst type of blood picture have invariably terminated fatally.

The chief significance of this test lies in the fact that it helps us to determine how the patient is handling his disease and, even if, by means of it, we cannot look very far into the future (and in this respect it shares the fallibility of our other prognostic criteria including roentgenographic findings), there are enough pressing problems at hand when we can utilize whatever aid is made available through a study of the blood.

A good blood picture has been found to parallel a healed lesion or one well along the course of healing and, although this is not a guarantee that the lesion will not show a recrudescence at any future date, observa-

tions here tend to indicate that with improvement noted on clinical and X-ray findings and a blood picture which returned to normal, the odds are more in favor of the patient's standing up under increased activities than when a change of treatment is instituted without due regard to the blood findings.

In the management of cases under artificial pneumothorax treatment, it was found that the blood picture may be used as an aid in estimating the effectiveness of collapse. In many instances after the lung is collapsed, we have to rely solely on our clinical findings, since the lesion in the collapsed lung can no longer be visualized on the roentgenogram. A tendency of a septic blood picture to become nonseptic is a good indication that the pneumothorax is affecting the lesion favorably. A failure of the blood picture to show normal values after a reasonable length of treatment with pneumothorax should, even in the presence of definite clinical improvement, excite one's suspicion as to the possibility of failure of healing of the lesion in the collapsed lung or the presence of some disease in the contralateral lung.

The difficulties in judging activity of a lesion by means of the roentgenogram is well appreciated by practitioners in tuberculosis and we are daily confronted with such problems. The dicision as to whether a thoracoplasty should be performed in a given case depends to a large extent on our ability to ascertain the nature of the lesion in the contralateral lung. It is obvious that given a septic blood picture in bilateral tuberculosis, one could not determine whether the lesions are active in both or only in one lung. However, when the blood picture is nonseptic or approaching the nonseptic type, there is less likelihood of activity on either side. In such an instance, the blood picture could be used to supplement X-ray and clinical findings when they suggest a quiescent lesion in the contralateral lung.

In the course of this study, it became quite evident that to be of practical value the blood has to be studied routinely and at frequent intervals. It was found that the test could be utilized not only in those cases which presented problems from the outset but also in cases where blood studies appeared at first quite superfluous. Far-advanced, apparently hopeless cases have improved in the course of time to such an extent that they became problems in further treatment, and series of blood pictures could have aided materially in the solution of some of these problems.

It was also found that much valuable information would be lost if one

was to take notice only of blood pictures with marked elevations of the cell counts. In fact, spectacular rises in the cell counts were few when the counts were done under basic conditions. Thus it was found that, whereas 81 out of a series of 98 basic counts in a group of 98 tuberculous patients showed total cell counts above 7,000, only in 45 instances the counts ranged between 8,000 and 12,000 and only 18 showed total counts between 12,000 and 18,350. However, the greatest number of counts in this group, though not markedly elevated, were definitely above normal when compared with leucocyte counts done on normal individuals under basic conditions. In a series of 44 basic counts taken in a group of 10 nontuberculous young women (student nurses), the total counts ranged between 3,400 and 8,750; only 9 counts showed elevations above 7,000; and but 2 instances, cell counts over 8,000. The variations in the differential counts between the tuberculous and nontuberculous groups were also very significant. Only 3 counts out of 44 in the nontuberculous group showed polymorphonuclears above 5,000 against 74 out of 98 in the tuberculous group with polymorphonuclears above 5,000 per cmm. of blood. The monocyte-lymphocyte ratio was above 0.3 in 11 instances out of 44 in the nontuberculous group and in the tuberculous group it was increased in 83 out of 98 cases.

The following cases were chosen to illustrate the application of the leucocytic picture in the management of the tuberculous patient.

Case 1: Female, age 30, came to the sanatorium February 10, 1932, with widespread bilateral pulmonary tuberculosis. Onset dated back to May, 1925, with sudden haemoptysis while at work. The patient had sanatorium treatment for 18 months (1928–1929).

On admission she complained of cough, expectoration, loss of strength and loss of weight. Sputum was positive (Gaffky 2 to 8). Temperature ranged between 98° and 100.4°F. Pulse between 80 and 100.

Her clinical course at the sanatorium was rapidly progressive. Cough became very troublesome; sputum increased to 8 ounces in 24 hours. She had profuse night-sweats. Temperatures were high. Death occurred August 30, 1932.

Autopsy showed extensive tuberculosis of both lungs with cavitation in both upper lobes and right median lobe. There was much caseation and fibrosis in both lungs, miliary and confluent miliary tubercles in some areas, and on the whole very little functioning lung tissue left.

This was an obviously hopeless case and the blood picture was in agree-

ment with clinical, X-ray and autopsy findings. The case is presented here to illustrate the worst type of a blood picture. There was a striking difference between the counts taken during the first two months after admission and those taken during the last two months. The polymorphonuclears were high throughout, indicating a high degree of abscess-formation. But in the first four counts the lymphocytes were above 2,000 in three instances, showing that there was still some tendency toward repair. Counts taken during the last two months showed a marked drop in the lymphocytes which may be looked upon as an "exhaustion of reparative forces." All other terminal cases in this series showed a similar type of blood picture.

Case 2: Female, age 29, admitted to the sanatorium January 7, 1932, with far-advanced bilateral pulmonary tuberculosis involving the entire left and the upper part of the right lung. Onset dated to February, 1931. She "caught cold," and began to cough and raise about 2 ounces of sputum in 24 hours.

On admission, she complained of nausea, poor appetite, tired feeling, cough and expectoration. Sputum purulent, positive (Gaffky 10). Temperature ranged between 98° and 100.2°F. Pulse between 80 and 100.

Her course at the sanatorium was characterized by periods of well-being alternating with exacerbations of symptoms. A roentgenogram taken early in April, 1932, showed slight reparative tendencies in the lungs. Later in the same month a bronchopneumonic lesion developed at the right base and progression was also noted on the left side. In July, 1932, the right showed marked clearing, with some improvement on the left. In November, 1932, a phrenicectomy was performed on the left with the hope of aiding the more involved side. Following the operation, symptoms continued, but periods of well-being appeared more frequently. Serial X-rays continued to show increased involvement in some areas and clearing in others. At the writing of this report (January, 1934), the patient's general condition appears somewhat improved.

The prognosis in this case was not as clear-cut as it was in the first case. This is the type of patient one would like to observe for some time and follow with serial X-ray films before venturing a prognosis. However, the question, "Has the patient a chance?" is put up repeatedly to the attending physician and he is obliged to answer it sooner than he would like to. From clinical and X-ray standpoints, it appeared as if the outlook in this case was poor even for the near future but, as it was noted, the patient is still holding her own two years after admission.

Blood studies were begun in this case in March, 1932, and, if the blood findings of the first 2 or 3 months were considered in formulating the prognosis, perhaps a more hopeful view could have been taken. Although the polymorpho-

nuclears were high in her blood pictures, the lymphocytes were also elevated in many instances. This tends to indicate that the lesions seen on the roentgenogram were not representing abscess-formation exclusively but that they also contained the elements which lead to repair. The tendency toward repair was also reflected in the blood pictures during the remaining period of observation. (The lymphocytes were above 2,000 in 18 of 26 counts.) The blood findings in this case from the beginning showed that the patient still had a "fighting chance."

Case 3: Female, age 27, was admitted to the sanatorium September 30, 1931, with moderately advanced pulmonary tuberculosis. Her illness began in the fall of 1929 with cough and expectoration, loss of weight and strength. In January, 1930, she noted some clotted blood in her sputum. In April she had elevation of temperature, sweats and chills. She was then diagnosed as tuberculous and advised sanatorium treatment. She began to take bed-rest, first at home, and later at a sanatorium where she remained until her admission here.

On entering this sanatorium her expectoration was scanty but it was still positive. Her general condition was good. Her temperature ranged between 97.8° and 98.6°, and pulse between 70 and 80. On the whole, the picture was that of a fairly quiescent case of pulmonary tuberculosis.

Since the patient already had a prolonged course of bed-rest (over 16 months), it was felt that it was safe to allow her to become ambulant shortly after admission. Early in December, 1931, she began to cough more. Physical signs in the chest increased and an X-ray film of December 11, 1931, showed progressive disease, especially on the right, where it appeared as the caseopneumonic type.

Patient was returned to all-day bed-rest, which was continued till October, 1932. On January 21, 1932, X-ray showed retrogressive changes. From then on, serial X-ray films showed a constant reparative tendency. There was also gradual improvement in the patient's general condition. Bacilli in the sputum gradually diminished and sputum proved negative in November, 1932.

The patient was discharged from the sanatorium at her own request November 22, 1932. She has since been examined in our follow-up clinic a number of times. Serial X-ray films show further clearing and her general condition is good.

Blood studies in this case were begun in March, 1932. The reparative tendencies noted on the roentgenogram were reflected in the peripheral blood by an elevation of the lymphocytes. However, the polymorphonuclear leucocytes were high in numbers and continued to be elevated until July, 1932, thus indicating an unstable lesion with some degree of abscess-formation. From then on, the polymorphonuclears remained below 5,000, and the lympho-

cytes somewhat above 2,000 which may be interpreted as a definite tendency towards stabilization and healing of the lesion.

It is interesting to note that the blood pictures in this case continued to show evidence of abscess-formation for seven months after improvement became evident from clinical and X-ray findings. Obviously the leucocyte counts furnished us with information not disclosed by our other methods. This would tend to indicate that the progress of the case could be more accurately followed if the blood pictures were included among our other criteria for judging activity in tuberculosis. The blood picture would serve as an added safeguard, especially when an increase in the patient's activities is contemplated.

Case 4: Female, age 28, admitted to the sanatorium September 30, 1931, with far-advanced pulmonary tuberculosis involving chiefly the right lung, with a small amount of infiltration in the left between hilum and apex. She had an haemoptysis shortly after admission to the sanatorium. Artificial pneumothorax was instituted on the right. The haemoptysis was controlled. Pneumothorax was continued. A moderate pleural effusion developed February, 1932, which gradually became absorbed. Patient improved clinically. Serial X-ray films showed a good degree of collapse on the right and retrogression in the small lesion on the left. After 14 months on all-day bedrest, the patient was allowed up for meals in the main dining-room. On February 12, 1933, she had an haemoptysis of 3½ ounces and a few small haemoptyses during the next 3 days. An X-ray of the chest taken on February 13 showed an almost complete collapse on the right, and on the left there was a suggestion of slight new infiltration. On May 15, 1933, the patient had an haemoptysis of 10 ounces. X-ray of chest showed definite increase in the lesion on the left. It became increasingly evident that the bleeding came from the left lung. On May 26, 1933, artificial pneumothorax was instituted on the left. The patient had a few small haemoptyses between May 26 and June 2, and none afterward.

Blood studies in this case were begun five months after artificial pneumothorax was instituted on the right. The leucocytic pictures showed that even after 12 months of what was considered an effective collapse on the right (at about the time when the patient was first allowed up for meals) the blood counts still failed to show a definite tendency to become normal. The polymorphonuclears were elevated frequently (polymorphonuclears above 5,000 in 15 out of 21 counts), and the monocytes likewise showed some increases. The leucocytic picture suggested a smouldering process somewhere. The subsequent events in this case proved it to be in the contralateral lung. It is true that from the blood picture one cannot tell definitely where the active process is located, since it is well known that activity may continue even

in a collapsed lung. However, the blood findings may serve as a signal to call attention to the fact that all is not as well as it appears.

Case 5: Male, age 27, admitted to the Sanatorium January 22, 1932. Onset of disease dated back to May, 1931. It began with cough, expectoration and elevations of temperature. Profuse haemoptysis in August, 1932. The patient's strength became poor and he was troubled with nausea and vomiting.

On admission there was extensive involvement throughout the left lung, with cavity-formation in the upper lobe, and also infiltration in the upper third on the right. The patient had a small haemoptysis on January 25, 1933. On February 13, 1933, artificial pneumothorax was instituted on the left side. The left upper lobe was adherent and the cavities remained open. The patient was in too poor condition for thoracoplasty and, besides, there was also contralateral involvement. In spite of failure in its main objective, the collapse of the cavities, the pneumothorax was continued, and proved to be of great benefit. In November, 1932, a left phrenicectomy was performed. This was planned as an aid to the pneumothorax. The idea was to eliminate to a certain extent the pull on the mediastinum caused by the movement of the hemidiaphragm, and thus perhaps allow the cavities to contract. This, however, was effective to but a small degree. The patient's general condition continued to improve and he gained in weight and strength. The sputum, however, was persistently positive, and the cavities in the left upper remained uncollapsed. In November, 1933, it was felt that the patient was in good condition for thoracoplasty. In December, 1933, a two-stage thoracoplasty on the left was performed with effective closure of the cavities.

The first blood count in this case was done a day before the artificial pneumothorax was begun. The polymorphonuclear leucocytes were markedly elevated, indicating much abscess-formation. They continued relatively high for several months, but there was a striking drop following the institution of artificial pneumothorax. This was a good sign. This prompt improvement in the blood picture probably reflected the beneficial influence of the pneumothorax on the involved areas around the uncollapsed cavities, as well as on the lower lobe which also showed much tuberculous infiltration. The blood picture in this case supplied objective evidence of the efficacy of the treatment, early, and at a time when information gained through clinical and X-ray examination was still equivocal. Later in the course of treatment, improvement in the patient's condition became so striking that no one would question the value of the pneumothorax in this case.

Early evidence of the good effects of a pneumothorax is particularly important in this type of case. It may serve to encourage the attending physician to persevere in the pneumothorax, even though at first it appears to be ineffective, and such perservance may in turn obviate too early surgical intervention.

Case 6: Male, age 28, admitted November 6, 1931. Onset in August, 1925, at which time patient had cough, expectoration and night-sweats. He had a sanatorium residence of 15 months, followed by improvement. Worked for 2 years, had a relapse, and in the fall of 1929 was readmitted to a sanatorium where he remained till his transfer here. He had a right phrenicectomy October 30, 1930. Was on all-day bed-rest for 14 months and became ambulant in June, 1931. His chest findings disclosed far-advanced bilateral pulmonary tuberculosis with extensive involvement of both lungs, more marked on the right and with a huge cavity in the right upper lobe. Temperature 98°, pulse 70 to 90, weight 150. Sputum about 2 ounces in 24 hours, positive for tubercle bacilli. He was ambulant for two months; then had a relapse which necessitated his return to all-day bed-rest. His sputum at times was very profuse, 8 to 16 ounces in twenty-four hours. His general condition remained good. It was quite obvious that if a closure of the large cavity could be effected, we would rid him of a great obstacle to his improvement. But the contralateral lung was well seeded throughout and it was feared that some of the lesions there might be active. After repeated consultations with the thoracic surgeon and the roentgenologist covering a period of 12 months, a thoracoplasty was finally recommended. The contralateral lesion had shown no apparent change during that period and it was felt that the opportunity for operative interference might be lost entirely if we waited longer. A two-stage thoracoplasty was performed in June, 1933. The patient stood the operation well, and at this writing (January, 1934) there is still no appreciable difference in the lesions on the left on clinical or X-ray examination.

The blood picture in this case is of interest inasmuch as it pointed to the probability of the lesions on the left being inactive at a time when much doubt was entertained as to the status of the lesion as judged by clinical and X-ray findings. Blood studies were begun in this case 2 months after the patient had his relapse and it was found that in spite of his cough and large amount of sputum, his blood counts showed the polymorphonuclears elevated in only 6 out of 20 counts and the monocytes in 11 counts. On the whole, therefore, the blood picture favored the probability of an inactive lesion on the left. This information as to nature of the lesion could have been utilized as a point in favor of earlier operative interference. At the writing of this report, additional surgical work is contemplated in this case with a view of effecting a more complete closure of the cavity on the right which failed to close following the previous operation. Less fear is entertained at present with regard to the lesion in the left lung. A series of 6 blood counts done recently (December 22 to January 6) furnish additional assurance that the lesions on the left side are inactive. The total counts ranged between 6,025 to 8,300, polymorphonuclear leucocytes between 2,709 to 4,980, lymphocytes between 2,259 to 2,908, and monocytes between 235 and 648.

SUMMARY

A series of leucocytic pictures in a group of tuberculous patients was correlated with clinical and X-ray findings. The observations made tend to show that the leucocyte count is of definite value in the management of the tuberculous patient. It may be used as an aid in evaluating treatment, in selecting patients for collapse therapy and to a certain extent in gauging the prognosis in a given case. It was found that not only marked elevations of the leucocytes but even moderate elevations of the white cell count are of definite clinical significance. The importance of doing the blood counts under basic conditions was emphasized and the result of a small series of basic leucocyte counts obtained in a group of normal individuals was presented.

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THE LONGEVITY OF TUBERCLE BACILLI IN SEWAGE AND STREAM-WATER[1,2]

CHESTER RHINES

While investigating the longevity of tubercle bacilli in soil and in association with other microörganisms, the observation was made that the *Avian 531* tubercle bacillus, which is being used extensively by investigators in the field of tuberculosis, was capable of surviving for a long period in highly contaminated liquid media. The method of investigation was found to be well adapted to study of the death rate in sewage and in stream-water. The tubercle bacillus was inoculated into sewage and stream-water and its persistence satisfactorily noted for three months.

Sewage from the New Brunswick, N. J. sewer outlet and stream-water, head-water of the Raritan River, were furnished by the Sewage Department at the New Jersey Agricultural Experiment Station. A suspension of *Avian 531* was made by shaking bacteria from a glycerol-agar culture with sterile gravel and water. The sewage and stream-water were equally inoculated with this suspension. Twenty-cubic-centimetre samples were placed in test-tubes, the depth of liquid being about 5 inches. These tubes were kept in a dark place at room temperature during the summer months. The tubes were not molested until used to count the tubercle bacilli. Uninoculated control samples of the sewage and stream-water were also kept. At various intervals tubes from all four samples were plated by a special selective method devised for counting *Avian 531.* The plating method consisted of treating the samples with an equal volume of 2 per cent sodium hydroxide for ten minutes, neutralizing, and plating on glycerol-agar containing crystal-violet. An important factor in the success of this plating method has probably been the special type of dilution blank. The inoculum was always spread on the surface of the agar medium in 1 cc. of a very dilute

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agar. The tubercle bacilli seemed to initiate growth unusually well when embedded in this shallow layer of agar medium.

Agar medium

Peptone	5.0 gm.
Beef extract	3.0 gm.
Glycerol	50.0 cc.
1 per cent alcoholic crystal-violet	0.3 cc.
Agar	20.0 gm.
Water	1000.0 cc.

Final reaction pH 7.0

Dilution blanks

One part of above medium
Four parts of water

The melted agar was poured into sterile plates and allowed to solidify before the plates were inoculated. The dilution medium was liquefied and held at 40°C. during the plating process. Only tubercle bacilli developed on the plates from which the counts were obtained. The uninoculated control samples yielded colonies only at dilutions too low to interfere with the counts of *Avian 531*. The tubes were thoroughly shaken to disperse all bacteria before plating except for the counts of the suspending liquid on the 73rd day. No counts were made after 93 days.

TABLE 1

Survival of Avian 531 in sewage and stream-water

DAYS AFTER INOCULATION		SEWAGE	STREAM-WATER
0		49,000	48,000
8		101,000	150,000
12		65,000	200,000
34	(Duplicate determinations)	29,000	48,000
34	(Duplicate determinations)	25,000	63,000
73		1,400	4,200
73	(Supernatant fluid)	400	940
93		140	9,400

The counts were listed in numbers per cubic centimetre of liquid. Each count was based on the average of 6 plates. The results are reliable, for they are consistent and the plates checked well. The increased counts obtained on the eighth and twelfth days may not indicate

an actual increase in the number of bacilli present. Increased dispersion may have occurred following the suspending of the bacilli in liquid. The important and undeniable conclusion is that the death-rate was slow. The bacteria did not completely settle out of the undisturbed liquid in 73 days. The indicated death-rate in sewage is slightly higher than in stream water.

No bacteriological or chemical studies were made of the sewage and stream-water used. The sewage was medium-weak. Turbidity and pellicle-formation indicated vigorous microbial activity. The tubercle bacilli in the sewage were probably deprived of dissolved oxygen, at least for a period after introduction into the sewage.

To demonstrate further the survival of *Avian 531* in biological competition with other microörganisms, the following observations are presented. *Avian 531* was suspended in test-tubes of a mineral medium containing ammonium sulphate, sodium chloride, magnesium chloride, and potassium-phosphate buffer. No energy source was added except the organic matter introduced with the tubercle bacilli. Some of the cultures were kept pure and others were inoculated with a soil suspension. In this clear, liquid medium Mycobacteria could be stained and distinguished from non-acid-fast organisms. The tubes inoculated with soil had profuse bacterial and protozoan populations. After 120 days the Mycobacteria had disappeared from none of the tubes. At times it appeared that the acid-fast bacilli were in a more disintegrated state in the mixed culture than in the pure culture. Danger of confusing débris of soil bacteria with débris of tubercle bacilli makes these observations of doubtful reliability. The cultures were plated on two occasions and the *Avian 531* count determined. The following numbers were found per cubic centimetre of culture:

TABLE 2

Survival of Avian 531 in a mineral medium

	PURE CULTURE OF *Avian 531*	*Avian 531* CULTURE INOCULATED WITH SOIL-INFUSION
60 days after inoculation	15,000	2,200
120 days after inoculation	28,000	0 (lowest dilution was 1/20)

The ability of *Avian 531* to survive in a highly contaminated liquid was thus clearly revealed. A slow destructive action by the soil microorganisms was also indicated.

It seems to be definitely established that tubercle bacilli are defecated by tuberculous people. Infection by ingestion is also well established. The length of time that tubercle bacilli are able to survive in sewage and in streams can thus be a factor in the spread of the disease. The slow development of the disease and its characteristic tendency to form latent lesions in victims are reasons that it would be difficult or impossible to trace infection back to water supply.

Avian 531 is rapidly destroyed by chlorine. In sewage, 91 parts of available chlorine per million reduced the plate count numbers from 47,000 to 20 per cubic centimetre in thirty minutes. Apparently all tubercle bacilli are not susceptible to chlorine treatment. Tubercle bacilli are commonly isolated from infected materials after chlorine-liberating chemicals have been used to destroy contaminants. Tubercle bacilli are generally considered resistant to chemical sterilizing agents.

Experiments of the type described here require careful selection of the strain of tubercle bacilli. The experiments could not be repeated with the *H37* (human) and *Ravenel* (bovine) tubercle bacilli, because these organisms did not resist sodium hydroxide sufficiently well. The *Avian 531* strain is similar in many ways to other tubercle bacilli, but it would be speculative to predict that other strains would survive in sewage and stream-water in a similar manner.

A number of investigators have demonstrated the longevity of tubercle bacilli outside of a host's body under a variety of conditions. Schalk (1) has presented evidence that avian tubercle bacilli infecting barn-yards survive the winter and infect animals pastured therein in the spring. He has also shown that tubercle bacilli survived in dead, buried fowls for at least one year. Williams and Hoy (2) have found bovine tubercle bacilli to survive well on pasture land, in faeces and in liquid manure. Maddock's (3) results show a long viable period in faeces, in soil and on grass. Tubercle bacilli in sewage have been demonstrated by Brown, Petroff and Heise (4), and by Cummins and Ackland (5). Conroy, Conroy and Laird (6) demonstrated the presence of tubercle bacilli in sewage and found that chlorine treatment was effective in ridding the sewage of these organisms.

SUMMARY

1. The *Avian 531* strain of tubercle bacilli has a very slow death-rate in sewage and in stream-water, as indicated by the selective plate-count method.

2. The suspended bacilli did not settle out of the undisturbed liquid in 73 days.

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MODERN CONCEPTS ON THE COLLAPSE THERAPY OF TUBERCULOUS PULMONARY CAVITIES[1,2]

B. P. POTTER

In spite of the pessimistic note recorded in the chapters on collapse therapy in Fishberg's (1) recent work, one is impressed with the value of collapse therapy from reading the voluminous literature on the subject that has accumulated in recent years. Doubtless, as more critical data are brought forth, the present overwhelming enthusiasm may prove unjustified. For the present, however, from observations of our own and those of others, we are willing to affirm that, in the moderately and far advanced cases, collapse therapy as an adjunct to the "rest cure" remains the most potent measure.

With this thought as a basis, we shall attempt to appraise the various forms of collapse therapy in the light of the place each holds, not as an individual procedure to be generally applied, but rather as parts of a wider program. Furthermore, it is our purpose in this paper to introduce a new procedure and stress concepts only occasionally referred to in the literature. Certain definite principles, to be discussed below, guide our work.

First, the infiltrative or acino-nodose form of pulmonary tuberculosis with negative sputum is treated by the usual hygienic regimen unless ulceration or progression takes place during the treatment (figures 1 & 2). When, however, a patient presents an infiltrative lesion with positive sputum and disputed evidence of cavitation he is placed in the small-cavity (2 cm. or less) group, in which collapse therapy is favored after a liberal period of bed-rest has effected little or no improvement. When the cavity is larger collapse in one of its forms is immediately resorted to unless there are other contraindications (figure 3). The danger of seeding from such cavities to the same or contralateral lung and the development of adhesions is too frequent an occurrence to favor the opinion stressed by some, namely, that a trial period of bed-rest be given

[1] From the Hudson County Hospital and Sanatorium, Secaucus, New Jersey.

[2] Read at a meeting of the Eastern Section of the American Sanatorium Association, October 6, 1933.

every cavity patient. Furthermore, in our experience, such cavities seldom close on bed-rest alone.

As a second basic principle, we contend that compression should be confined to the diseased portion of the lung. This is being more and more realized as is evidenced by the numerous papers on so-called selective thoracoplasty in the past two years. One can no longer contend that results are directly proportionate to the degree of collapse. It has been amply demonstrated that collapsible cavities can be closed with little or no sacrifice of normal lung tissue if one is patient (figure 4). Thus, in a series of 152 cases, subjected to pneumothorax by us, only

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Plate 1

Fig. 1A. E. A. 8,506. Male. Moderate productive cough, occasional positive sputum. X-ray shows bilateral closely-packed miliary infiltration, especially marked on left side, where, just beneath the clavicle, there is a small cavity. Temperature 100° to 101°.

Fig. 1B. Same patient. Fifteen months later. Showing almost complete clearing of the infiltration, with closure of cavity in left upper. Sputum negative, with a gain of 40 lbs. in weight. No cough or expectoration.

Fig. 2A. J. K. 8,645. Male. Admitted, showing on X-ray a diffuse density over entire left lung field, more marked over base. Multilocular cavities in 1st interspace. Right lung shows discrete foci distributed throughout the lung. Sputum positive. Fever between 101° and 103°.

Fig. 2B. Same patient. Eighteen months later. Showing clearing of density and absence of cavities; sputum negative. Twenty-five-pound gain in weight. Afebrile.

Fig. 3A. L. R. 8,610. Female. Bilateral mixed cavernous tuberculosis in each of the upper lobes. Marked retraction of left upper lobe. Sputum positive. Temperature between 101° and 103°. Troublesome cough and expectoration.

Fig. 3B. Same patient. Showing partial collapse confined to upper lobes with cavities closed. Sputum negative. No cough or expectoration. Weight normal for height and age. At home, but not working.

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6 per cent required complete compression. In an additional 40 per cent, closure of the cavity resulted with only a partial or selective collapse of the diseased lung, this in spite of the fact that adhesions were present in practically every case.

Third, the criterion for a satisfactory result must be X-ray evidence of a closed cavity. This point is being mentioned but not sufficiently stressed. Whatever value gain in weight, reduction in amount and change in character of sputum or negative sputum may have in the general outlook in any case, one should dismiss such evidence when evaluating the final results obtained by any form of collapse therapy. Only recently, in a paper before the Roentgenological Section of the

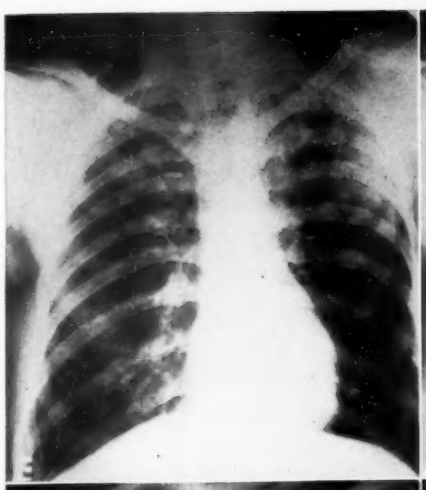

FIG. 1A

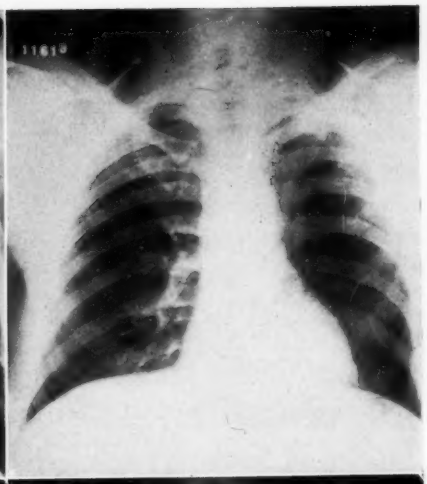

FIG. 1B

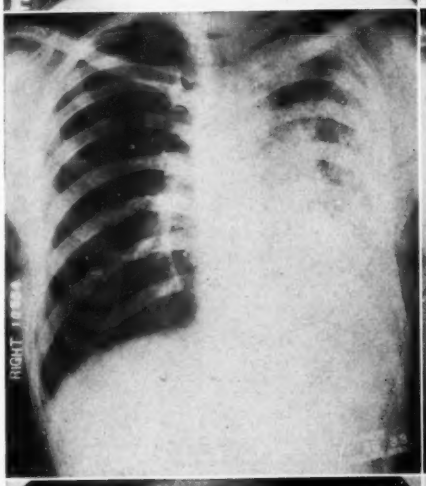

FIG. 2A

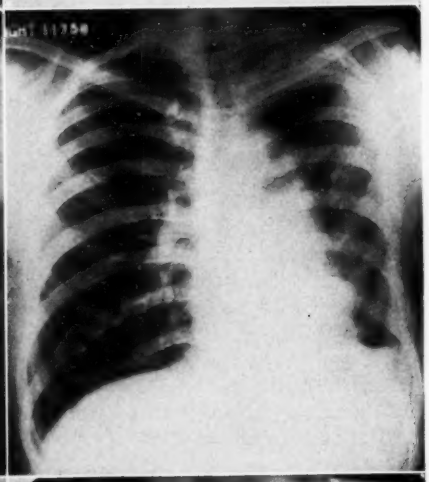

FIG. 2B

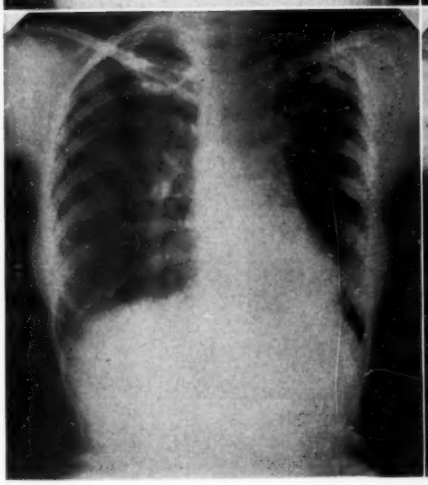

FIG. 3A

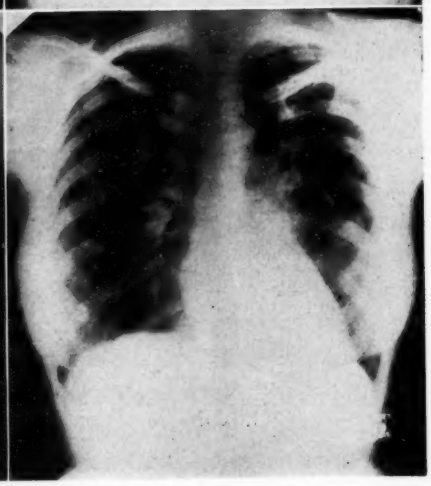

FIG. 3B

PLATE 1

New Jersey State Medical Society at its Annual Convention, McPhedran showed the fallacy of the belief that a gain in weight invariably indicates favorable progress of a case. As he pointed out, many patients will present X-ray evidence of progression of lesion while gaining weight.

Reduction of sputum and failure to find tubercle bacilli in such sputa must be equally disregarded as evidence of favorable progress unless corroborated by X-ray findings of a closed lesion. In our own experience, between 30 and 40 per cent of all cases under collapse therapy of one form or another present a negative sputum at intervals in the presence of

Plate 2

Fig. 4A. W. S. 8,749. Male. Mixed cavernous lesion confined to right upper lobe with scattered foci throughout both lungs. Sputum positive. Cough and expectoration. Temperature normal.

Fig. 4B. Same patient. Showing partial collapse. Confined to right upper lobe. Sputum negative. No cough or expectoration. Moderate gain in weight.

Fig. 5A. G. K. 8,778. Male. Plain film shows a hydropneumothorax on the right. The right upper half of the lung field is not collapsed because of an obliterative pleurisy. Within the uncollapsed portion of the lung there are numerous very small rarefied areas in the first interspace.

Fig. 5B. Same patient. Bronchogram. Outlines a large annular shadow within which is a lipiodol level, and situated in the 2nd interspace immediately beneath the pleura. While cavitation was thought to be present in the plain film in the 1st interspace none was suspected in location outlined by the lipiodol.

Fig. 6A. J. D. 8,481. Male. Partial pneumothorax confined to left upper lobe in which there is a semilunar cavity in the 1st interspace. Discrete foci throughout remainder of left lung and upper two-thirds of right. Mediastinum mobile and over to the right. Sputum positive, moderate productive cough, afebrile.

Fig. 6B. Same patient. Showing mediastinal structures in the midline, partial collapse of left upper lobe, cavity closed, sputum negative, no cough.

an open cavity. Whatever explanation one may have this apparent paradox nevertheless exists.

It should be evident, therefore, that we should exhaust all means of determining the presence or absence of cavity before placing a case in the group of favorable results. In our clinic we have added bronchography (2) (3) (4) as an additional measure by which we are able in a certain number of cases to assure ourselves of the presence of a cavity not suspected or made out in the plain plate (figure 5).

And as a final basic principle, we wish to stress the point of view that, in considering collapse therapy in any individual, one should think of all forms any one or combination of which may have to be applied at the appropriate time in that individual. This viewpoint has been more or

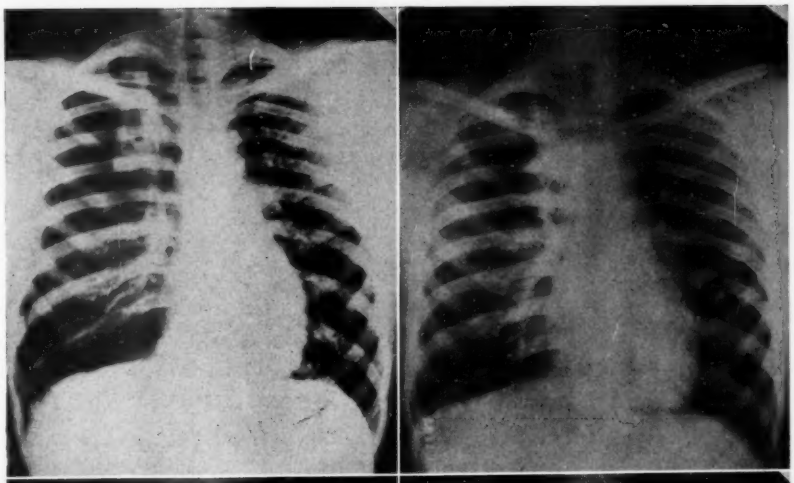

FIG. 4A

FIG. 4B

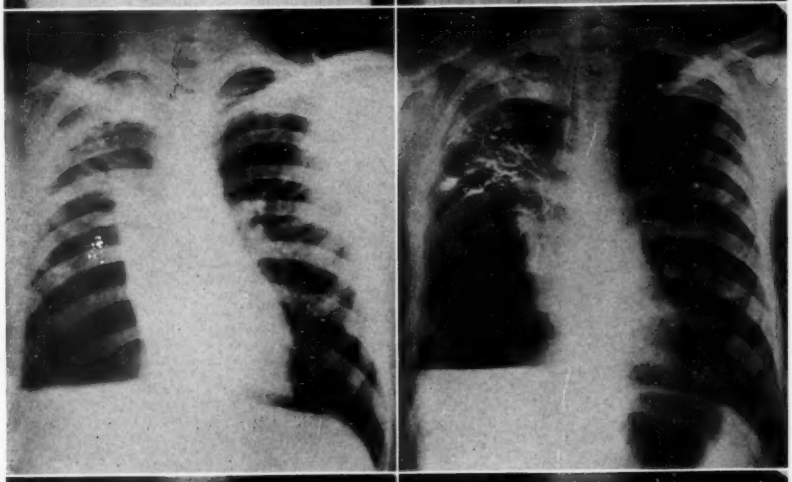

FIG. 5A

FIG. 5B

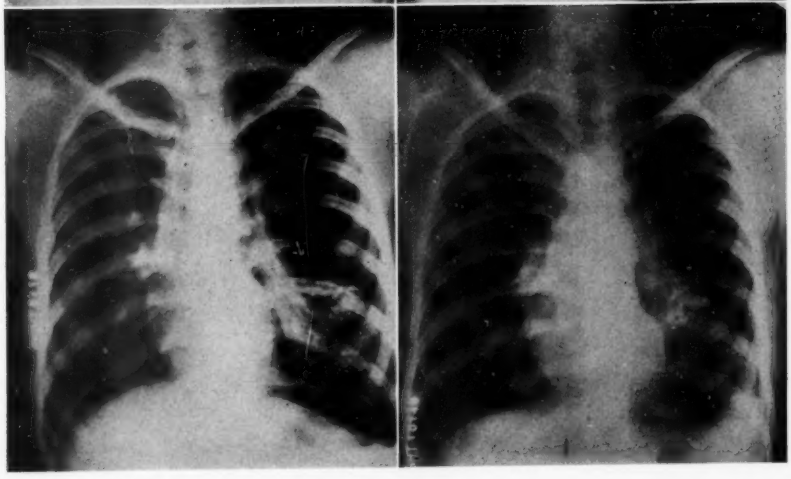

FIG. 6A

FIG. 6B

PLATE 2

less neglected as can be seen from reading the literature. Too often, one or another form of collapse is urged to the exclusion of the remaining procedures. This has resulted in instances in which patients are treated under a certain procedure, which, proving inadequate, yet is continued to the point where their condition will not permit another that may have given a favorable result if applied earlier in the course of treatment. This statement is well supported by our experience with 73 patients with far-advanced lesions in whom pneumothorax alone failed to close cavities. In these cases, satisfactory compression was obtained in 28.7 per cent when the pneumothorax was either supplemented by or abandoned for some form of formal surgery.

Plate 3

Fig. 7A. C. B. 8,481. Female. Mixed cavernous infiltration throughout right lung with two cavities, the lower occupying the 3rd interspace, the upper the first. Bronchogenic seeding in the left lower lobe. Sputum positive. Temperature between 100° and 101°, moderate cough and expectoration, and marked loss of weight.

Fig. 7B. Same patient. Showing closure of lower cavity, but enlargement of the upper.

Fig. 7C. Same patient. Spontaneous pneumothorax followed by sterile effusion. Greater collapse of lung, but upper cavity still open.

Fig. 7D. Same patient. Still greater collapse of lung, upper cavity closed.

Fig. 7E. Same patient. Lung reëxpanding in spite of frequent refills.

Fig. 7F. Same patient. Maintenance oleothorax induced. Sputum negative. No cough; gain of 30 lbs. in weight. At home though not working.

With this general introduction, we proceed to a discussion of the individual forms of collapse therapy.

ARTIFICIAL PNEUMOTHORAX

We consider pneumothorax the simplest and the most direct form of collapse therapy. We are aware that there are those who urge some form of phrenic operation on the basis that it is equally effective in the early moderately advanced case. Our experience, as will be seen from the discussion under phrenic interruption, has not justified such an attitude. The argument that pneumothorax carries with it a higher percentage of risk is equally unsupported, judging from the statistics of Berry (5) and Meyer (6) and those of our clinics. In a series of 225 initial pneumothoraces carried on for two years and for a total of 5,000 punctures, we have had only one case of pleural shock of transient nature, and one of embolism with a fatal ending. Bland effusions arose as a complication in 37.6 per cent and of these only 10 per cent required

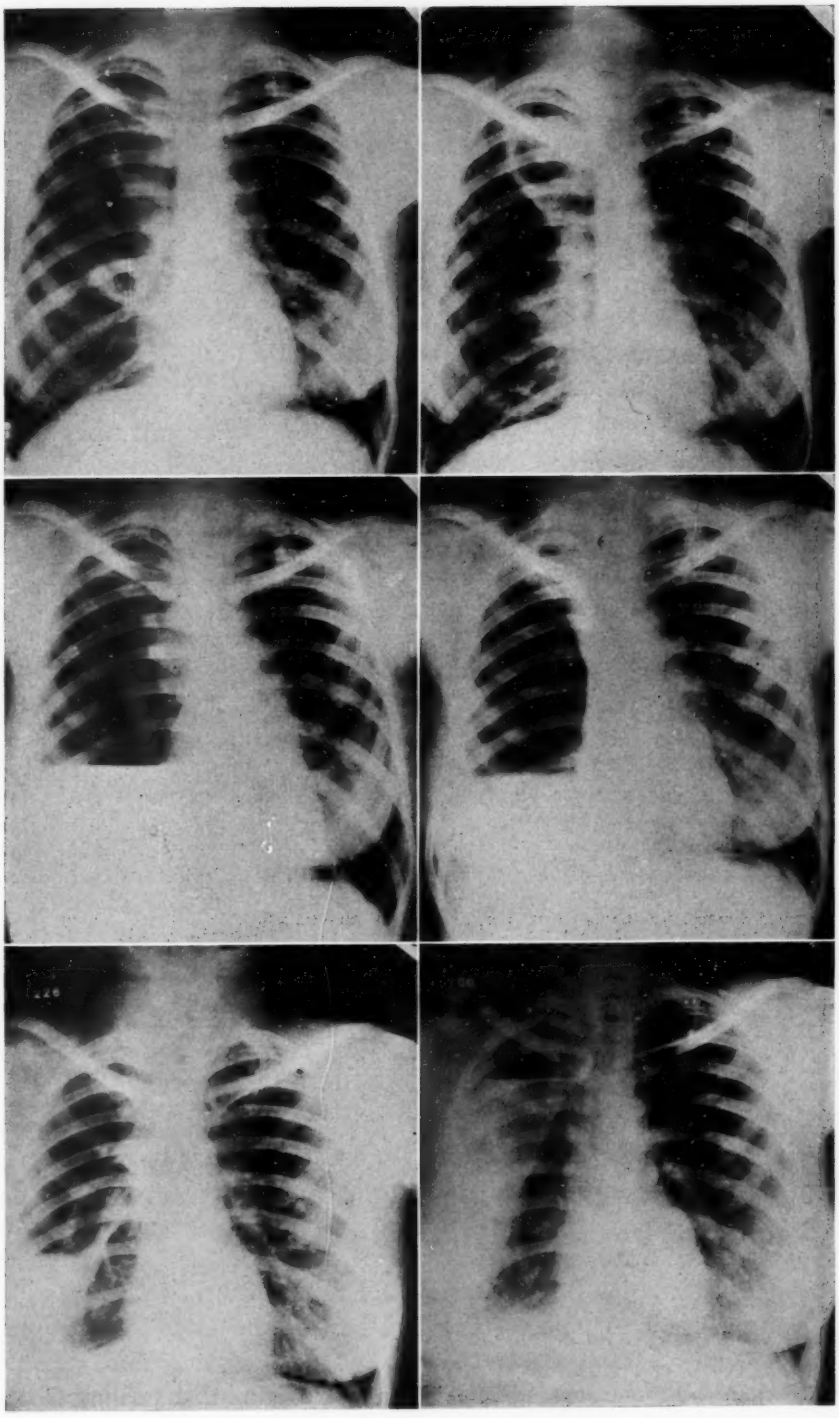

FIG. 7A

FIG. 7B

FIG. 7C

FIG. 7D

FIG. 7E

FIG. 7F

PLATE 3

aspiration. In but 10 cases or a little less than 5 per cent did empyema develop. When one compares these complications and their frequency with those that may follow phrenic exairesis, as pointed out by the above observers, one sees no appreciable difference in risk.

The spread to the contralateral lung that at times follows pneumothorax is again a factor not to be seriously entertained. In the first place, one cannot in every instance, when a spread to the contralateral lung has taken place, concede it to be due directly to the pneumothorax, for we know of instances in which such an unfortunate event takes place under routine treatment. In the second place, in a series of 49 patients subjected to some form of phrenic operation, spread to the contralateral

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Plate 4

Fig. 8A. M. S. Female, colored. Moderate cough, productive of positive sputum. Temperature between 100° and 101°. X-ray shows a partial pneumothorax on the left side and an exudative cavernous infiltration throughout the partially collapsed left lung. The huge cavity in the 1st and 2nd interspaces held out by wide short bands. Mediastinum stable.

Fig. 8B. Same patient. Artificial effusion induced.

Fig. 8C. Same patient. Several weeks after artificial effusion had been induced. Note resorption of effusion, closure of cavity and bands lengthened and narrowed. Afebrile. Sputum negative. No cough.

Fig. 9A. M. E. 8,807. Female. Afebrile. No constitutional symptoms. Cough productive of positive sputum. X-ray shows partial pneumothorax confined to the right upper and middle lobes. Large cavity in the 2nd interspace held open by adhesions hugging the 2nd anterior rib.

Fig. 9B. Same patient Immediately after a closed pneumolysis. Note small effusion over diaphragm.

Fig. 9C. Same patient. Five weeks after pneumolysis. Cavity collapsed. Sputum negative. No cough or expectoration.

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lung took place within a period of 48 hours in two, one resulting in death, whereas this accident occurred only six times in the series of 152 cases treated by pneumothorax.

On the other hand, when one inquires as to the favorable results with pneumothorax and compares these with results obtained in similar cases with phrenic interruption, one cannot help seeing the greater value of the former procedure. Thus in the series of 152 cases observed anywhere from several months to 2 years an effective collapse, by which we mean closure of cavity, was obtained in roughly 45 per cent. In the 49 cases in which no free pleural space could be found and in which a phrenic interruption was done, closure of cavity resulted in but 22 per cent. All in all then, we must conclude this discussion, urging that pneumothorax be considered the first procedure in any case eligible for collapse therapy.

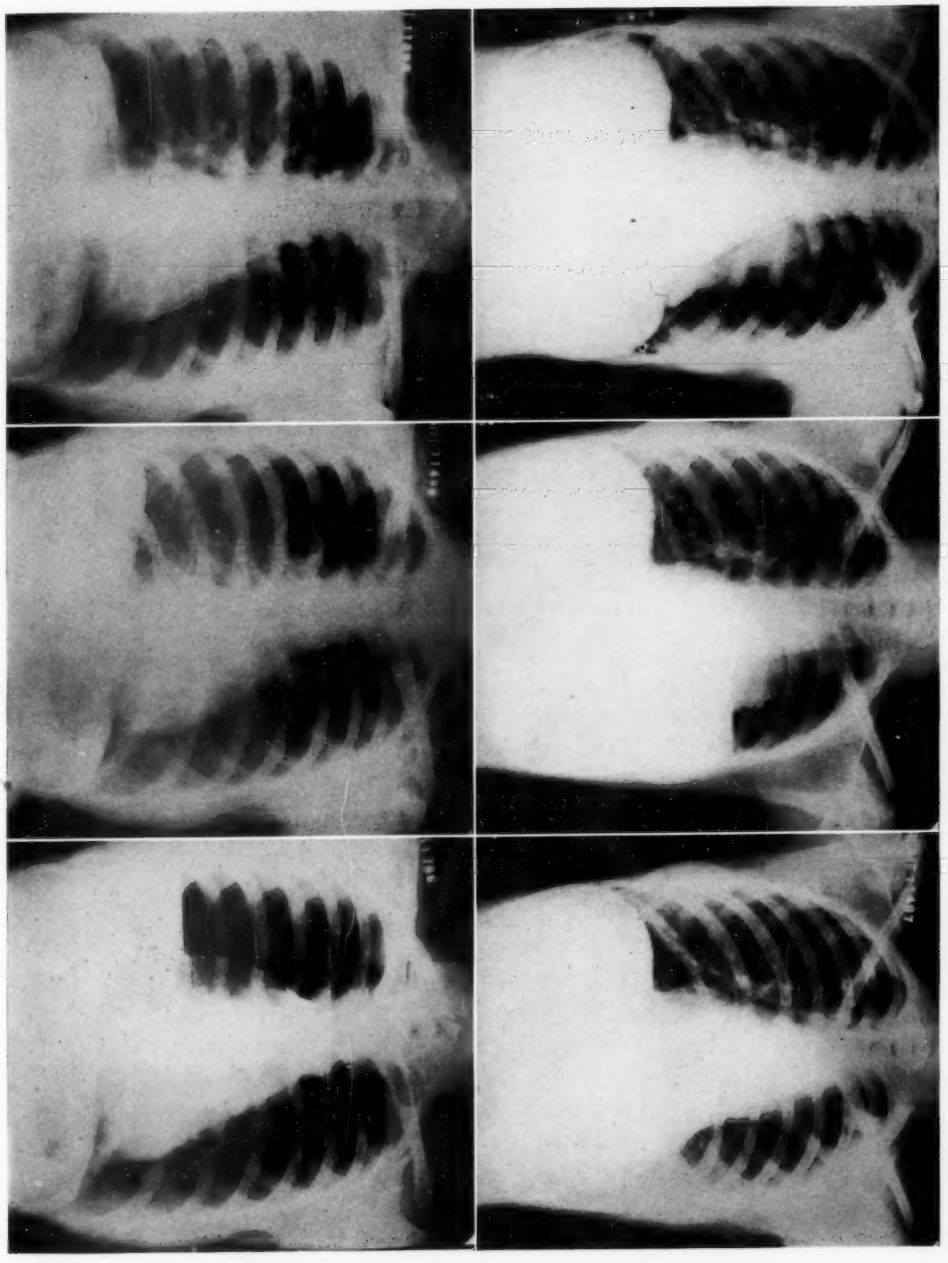


Fig. 8A Fig. 8B Fig. 8C

Fig. 9A Fig. 9B Fig. 9C

PLATE 4

Before leaving the subject of pneumothorax we should like to stress that an initial small quantity of air (150–250 cc.) and subsequent frequent refills of amounts ranging between 200 and 350 cc. usually result in a partial collapse confined to the diseased area and reduce the frequency of effusions.

OLEOTHORAX

It is well known that the mediastinum by shifting to the contralateral side may interfere with the satisfactory collapse of pulmonary cavities. The more one forces the pneumothorax when the mediastinum is excep-

Plate 5

Fig. 10A. S. W. 8,067. Male. Afebrile. Moderate cough productive of positive sputum. X-ray shows partial pneumothorax on left side, with huge cavity in 1st and 2nd interspaces in the outer zone. Right apex cloudy, and discrete foci throughout the remainder of the lung.

Fig. 10B. Same patient. Several months after phrenic interruption. Cavity collapsed. Sputum negative. Cough and expectoration practically nil. Patient at home.

Fig. 11A. P. S. 8,438. Female. Afebrile. No constitutional symptoms. Troublesome cough productive of positive sputum. X-ray shows two pneumothorax pockets on the left side, separated by a wide band in the 2nd interspace which is holding open a cavity. Discrete foci throughout the right, with mixed closely packed infiltrate above the 2nd anterior rib in the outer zone.

Fig. 11B. Same patient. After a partial thoracoplasty. Note collapse of cavity, due to release of wide bands and moderate clearing of infiltrate in the open lung. Sputum negative. Slight cough. Patient at home. Working.

Fig. 12A. A. R. 8,030. Female. In good general condition. Afebrile. Troublesome cough productive of positive sputum. X-ray shows large cavity occupying the 1st and 2nd interspaces and the outer midzone on the left side.

Fig. 12B. Same patient. Several months after phrenicectomy. Note collapse of cavity. Sputum negative. No cough or expectoration. Patient at home.

tionally mobile the more shifting one gets with little or no effect on the cavity. In such cases, it is far better to fix the mediastinum and then proceed with the pneumothorax. This can be accomplished by oleothorax.[3] We have utilized this procedure in a fair series of cases with very satisfactory results, but cannot go into details in this paper (figure 6).

Of course, as is known to all, oleothorax has been used to maintain an established collapse when for one reason or another the pneumothorax is being lost prematurely, and as a compression medium for firm-walled cavities. In selected cases a maintenance oleothorax is of decided

[3] Another way, with less danger of complication, is that devised by Burke (7) in the experimental animal, but not as yet given sufficient trial in the human being.

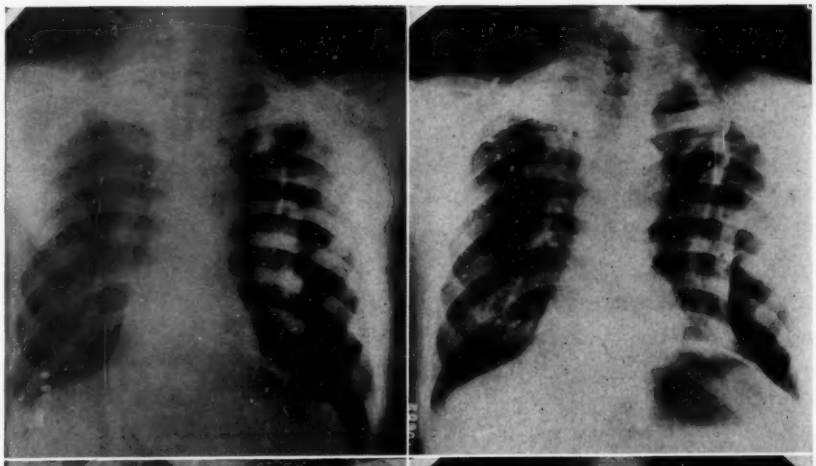


FIG. 10A

FIG. 10B

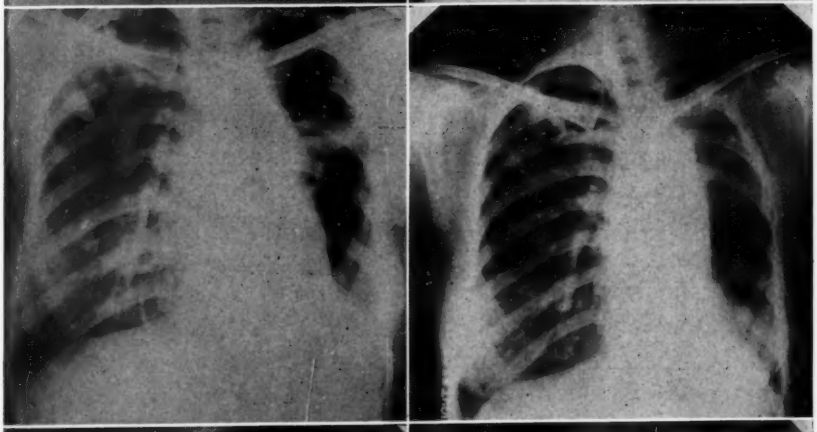


FIG. 11A

FIG. 11B

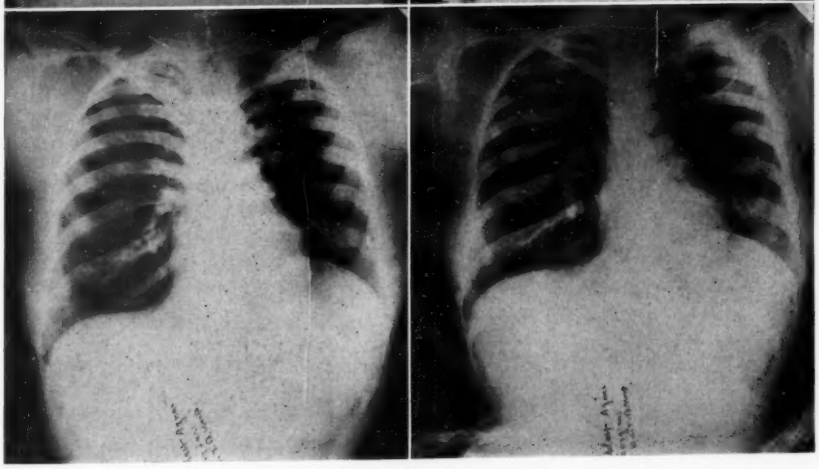


FIG. 12A

FIG. 12B

PLATE 5

advantage in that it assures a continued closed lesion without necessitating more radical surgery, at least for the time being. We have not used compression oleothorax because of the inherent dangers pointed out by Hayes and Brown (8) and others (figure 7).

For a long time, pneumothorax workers noted in occasional cases the collapse of a cavity after a spontaneous effusion had developed. It is on these observations that we attempted the production of an artificial effusion by oleothorax in cases presenting cavities either having firm walls or held out by adhesions not suitable for cauterization. The results have been very satisfactory in the small number tried. To describe the details of the procedure and its advantages and disadvantages would take us far from the theme of this paper. Such a report will be published in the near future (figure 8).

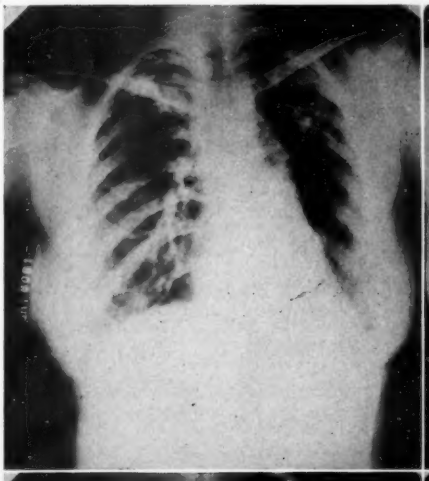
PNEUMOLYSIS

It is to be admitted that, in properly selected cases and in experienced hands, the severing of adhesions results in closure of cavities in a fair number, as was so well shown in the representative group reported by Welles (9). Whether, however, the procedure should be resorted to as frequently as it is in some clinics is very questionable. O'Brien (10) found occasion to do a pneumolysis in only 6 instances in 250 pneumothoraces. Our experience leads us to believe that between 2 and 5 per cent can be benefited by supplementing the pneumothorax with pneumolysis (figure 9).

One should not get the impression from the above statement that adhesions are encountered in so few cases. Quite the contrary, practically all far-advanced patients present adhesions. We have found, however, that with patience these can be stretched by pneumothorax in a large number of cases, resulting in closure of collapsible cavities. In the remaining, except for the 2 or 5 per cent suitable for pneumolysis, the cauterization of adhesions is fraught with danger either because the bands are wide and contain lung tissue, or too short, or are so located as to make approach difficult or impossible. In the latter group successful obliteration of cavity may be achieved in a small number by supplementing the pneumothorax with any of the following procedures:

1: Oleothorax, either for fixation of the mediastinum to be followed by frequent pneumothorax refills, or for induction of artificial effusions as mentioned above (figures 6 and 8).

FIG. 13A



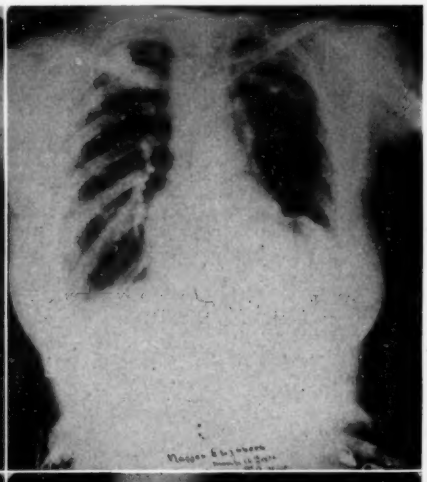
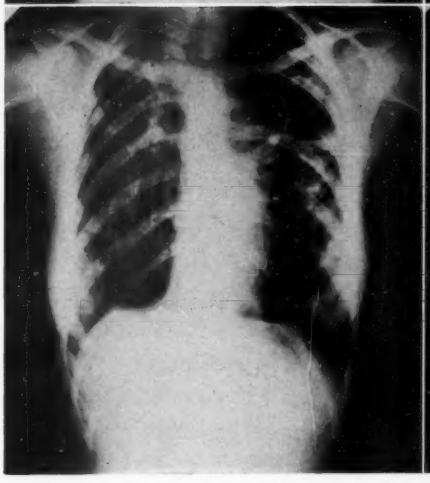


FIG. 13B

FIG. 14A



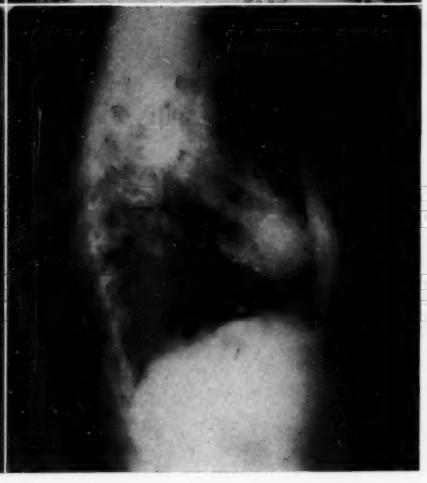


FIG. 14B

Plate 6

Fig. 13A. E. N. 7,848. Female. In good general condition. Afebrile. Moderate cough productive of positive sputum. X-ray shows multilocular large cavity in left upper lobe. Mixed infiltration above the first rib on the right side.

Fig. 13B. Same patient. After phrenic interruption. Note marked clearing of infiltrate in right apex.

Fig. 14A. J. Y. 8,277. Female. Showing bilateral diffuse mixed infiltration with a large cavity occupying the 1st and 2nd interspaces in the outer and midzone on the left side. Fluid level in cavity. Plain plate fails to reveal true location of cavity.

Fig. 14B. Same patient. Lateral view shows cavity occupying the paravertebral gutter.

2: Phrenic interruption which may give sufficient relaxation to the bands to allow approximation of the walls of a cavity by continued pneumothorax (figure 10).
3: Thoracoplasty (figure 11).

PHRENIC INTERRUPTION

It is our belief that, except in an occasional case, permanent interruption should not be established. As was remarked above, only 22 per cent of our series of phrenics resulted in closure of cavity. Furthermore, since, as will be shown, no one can fortell which case will respond, logic should dictate against permanent paralysis of a hemidiaphragm which later interferes to a greater or less extent with the normal function of the lower lobe when that is free from disease. We confine this procedure to three types of cases:

1: When pneumothorax is indicated, but a free pleural space is absent and one has reasons to believe that a favorable result may be expected (figure 12).
2: Cases for thoracoplasty in which the better lung, though somewhat diseased, is to be tested for its capacity to stand up when the worse side is partly relaxed (figure 13).
3: As a supplement to pneumothorax (figure 10).

The 49 patients in this series have now been observed between 9 months and 2 years, with an average of 14 months. Of these, the cavity closed in 11 or 22 per cent, and only 2 of the 11 presented basal cavities. Another interesting point is that 16 were good candidates for thoracoplasty, but in 5 the cavity closed following the phrenic interruption. This is a very important point to remember, for too often the surgeon insists on a thoracoplasty on the basis of discouraging reports concerning phrenics by some observers. In fact Ornstein (11) has gone so far as to discourage the practice of diaphragmatic paralysis entirely.

THORACOPLASTY

The methods discussed up to this point comprise a group of minor surgical procedures which if used intelligently will bring about closure of cavities in an appreciable number of the moderately and far advanced cases; and this at little risk. Furthermore each of these procedures is reversible.

Not so, however, with thoracoplasty, which is applicable in about 10 to 20 per cent of the cases in which the other methods have failed. It

holds out an immediate death-rate of anywhere from 3 to 10 per cent, and, because of its irreversibility, is coupled with dangers which by their remote effect add appreciably to the final death-rate.

Now, what can the tuberculous individual be offered with thoracoplasty? At the outset one should remember that in a variable number one will meet with uncollapsible cavities. A review of the recent literature would indicate that the average expectancy of satisfactory results as measured by closure of cavities is somewhere between 40 and 50 per cent. Of course, this figure can be directly influenced in any series of cases by the type of operation, the selection of the case, and the skill of the operator. Can this number of successes be augmented in the hands of the average surgeon? It would appear to us that attention to the following points would reduce the failures to a minimum.

First, as to selection of cases: We shall not dwell upon the type of case to be selected, for this is too well known to those engaged in tuberculosis work. We do wish, however, to stress a point so well expressed by Neuhof (12) when he says,

> The best indication for operation is the opinion of a well-trained physician who has cared for the patient for months or years, has followed the clinical course, has studied the evolution of the pathological process in the lungs, and has acquired a knowledge of the resistance to tuberculosis of that patient.
>
> His well-seasoned view is of far more decisive value than the details of symptoms, physical signs, or roentgenograms at any given time. It is not only presumptuous but also hazardous for a surgeon or a medical consultant to decide on the advisability of operation at a single sitting without full information from the physician who has been in attendance. Nothing is more to be deplored than snap judgment based on a series of roentgen-ray films. Contraindications can be more properly made by the physician or surgeon who sees the patient for the first time, but the indication rests largely on observations made over months and years. One should never forget that thoracoplasty is rarely if ever an urgent operation, and that further observation is imperative in any doubtful case. No matter how well informed or experienced in the field of pulmonary tuberculosis, the surgeon plays a rôle that is largely confined to the application of mechanical measures.

This view, with which we are in full accord, cannot be too strongly urged for acceptance by all internists interested in tuberculosis.

Second, the type of operation: We shall not enter into the debate still prevailing as to the comparative value of the complete paravertebral thoracoplasty and the partial or selective type now advocated. It is

evident from our general introduction that when possible there should be no interference with sound lung tissue. Recent innovations in the surgery of pulmonary tuberculosis is sufficient evidence of the growing dissatisfaction with the conventional thoracoplasty. When results are measured by closure of cavity one is impressed with the frequent disappointments. There should however be little or no difference of opinion when one plans the operation, bearing in mind that relaxation, as in pneumothorax, is the aim in thoracoplasty. When this is accomplished, approximation of walls of cavity will result when one deals with a collapsible cavity. While in pneumothorax such relaxation is brought about by a layer of air about the lung, the reverse is true in thoracoplasty in which the bony framework of the chest over the lesion must be freed. How extensive this costectomy should be seems to be the point of controversy. O'Brien (13) would have us believe that the resection of ribs should extend from transverse process to sternum (and in some cases even portions of the sternum) while Neuhof (14) (15) limits resections of ribs merely as an approach to the field of pathological involvement. We have had no experience with the former operation. The number of our patients operated upon by the latter method, however, is sufficiently large in our opinion to justify conclusions which may throw some light on this question.

Briefly stated, the operation of Neuhof, termed by him *pneumocavernolysis*, consists in making a parascapular incision extending from the level of the spine of the scapula to the anterior axillary line; the muscles are cut, and the scapula then lifted. Portions of ribs just sufficient to expose the underlying lesion (location of cavities is judged from a postero-anterior film) are resected, the intercostal structures and adjacent periosteum are dissected away and reflected medially in the form of flaps, and then an attempt is made to peel away by blunt dissection the thickened pleura overlying the cavity-bearing area. Finally the musculoperiosteal flaps are replaced and iodoform gauze packed snugly against the supposed site of cavitation. The muscles and skin are sutured except for the rent from which project the ends of the gauze packs which are kept *in situ* for several weeks.

We shall not go into all the objectionable points involved in this operation at this time. Our immediate concern is the fact that it entails too limited a resection of ribs, resulting in insufficient relaxation for closure of the cavity to take place. Furthermore, since the resection of ribs is done primarily to uncover the site of the cavity, collapse of which is

FIG. 15A

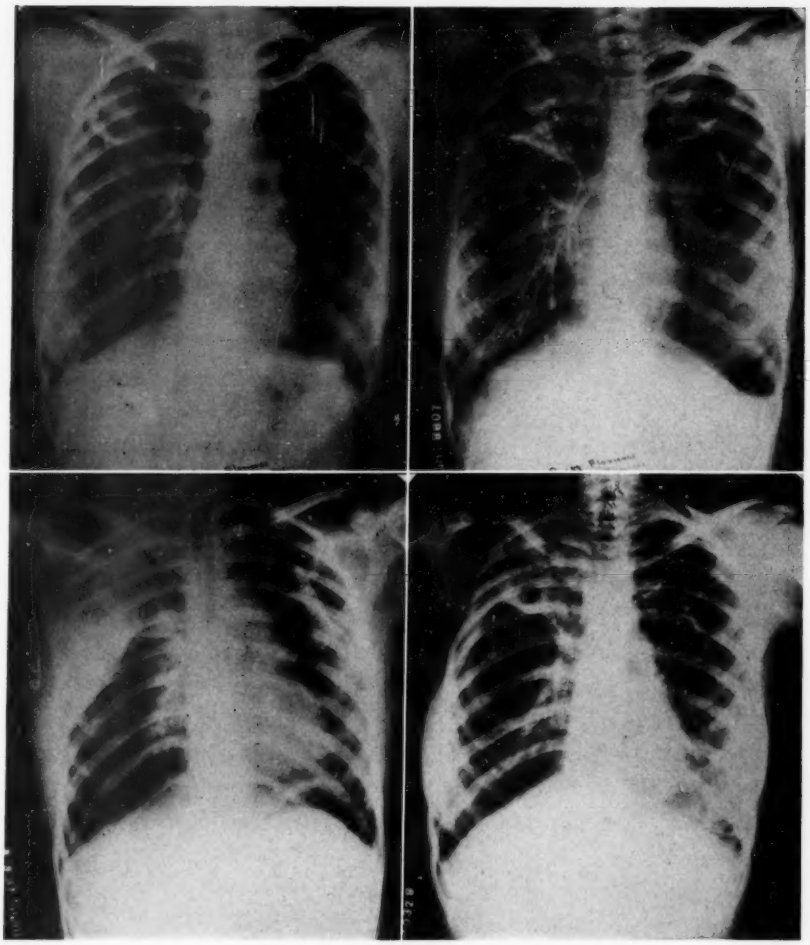


FIG. 15B

FIG. 15C

FIG. 15D

Plate 7

Fig. 15A. F. B. 8,521. Female. X-ray shows partial pneumothorax confined to the left upper. The right lung shows a small amount of air over the apex and an annular shadow in the 2nd interspace in the outer zone. Sputum positive. Afebrile.

Fig. 15B. Same patient. Bronchogram showing lipiodol level in annular shadow, thus proving it to be a cavity.

Fig. 15C. Same patient. After pneumocavernolysis, cavity mesially displaced. Note also pack, snugly placed against the cavity.

Fig. 15D. Same patient. After pack had been removed. Note that resection was confined to small portion of 2nd, 3rd and 4th ribs in the axillary region, proving entirely inadequate to produce sufficient relaxation for cavity walls to coapt. Also note marked thickening of pleura produced by pack over cavity.

attempted by packing against it, certain fundamental principles are often ignored. These are, first, the first rib which plays the predominant rôle in maintaining the thoracic cage is left untouched, and, second, the resection is not carried to the transverse processes so as to obliterate the paravertebral gutter, in which, as a rule, cavities are situated (figure 14). This is well illustrated in figures 15 where it will be seen that the first rib was not removed nor were the resected ribs carried far enough posteriorly. Of course it is obvious that the extent of rib removal is entirely inadequate, with little or no effect on the cavity.

It would seem to us, therefore, that to obtain the optimum degree of relaxation the operator should extend the resection of ribs to the transverse process and even include a part of the process, and the number and extent of ribs to be resected should correspond to the number and extent of ribs covering the cavity as determined from a lateral film. Of course, it is to be understood that the number of ribs to be removed cannot be determined with accuracy from the preoperative X-ray plate, for the location of the cavity is altered when the lung retracts downward and toward the mediastinum after the first stage. Whether the removal of ribs should be as extensive in any case as O'Brien indicates is to be questioned. We are, however, inclined to believe that following his logic one will not meet with the almost universal failures we have had with Neuhof's method.

Finally, the operator in planning the thoracoplasty should keep uppermost in mind the fact that patients coming to operation have, as a rule, been sick for years and cannot therefore withstand extensive surgery at any one time.

SUMMARY

1. Certain basic principles underlying collapse therapy in general are discussed.

2. The value of the various collapse methods is indicated, and the place each holds in the obliteration of tuberculous pulmonary cavities is stressed.

3. The induction of artificial effusions is recommended and its value in the collapse of cavities is pointed out.

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ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF PROGRESSIVE MINIMAL PULMONARY TUBERCULOSIS[1,2]

J. ARTHUR MYERS AND IDA LEVINE

In the earlier days of artificial pneumothorax work in this country, one frequently read statements to the effect that patients with minimal pulmonary tuberculosis should be given ample opportunity for their disease to show improvement on strict bed-rest before recommending collapse therapy. In fact, many workers still cling to this view. However, statements have appeared from time to time which have encouraged the extension of artificial pneumothorax to the early case. In writing of this method of treatment a number of years ago, Krause (1) said: "Time brings no dimming of its repute. Enlarging experience only adds to its lustre. Experience suggests also that its scope will enlarge; that after ten years of trial and experiment we are settling down into a period of its more intelligent employment which will lead to its further development." More recently, Brown (2) said: "The only objection to the early employment of this method is the possible occurrence of complications; but the successful advance in the treatment of such complications makes them now of far less moment, and further they are much less likely to occur in the early cases." Again he (3) says:

It is highly likely that in the future artificial pneumothorax will be induced earlier in many instances. Economically important, such a method would no doubt return many patients far sooner to work for it would hasten the disappearance of tubercle bacilli in the sputum. The length of residence in the sanatorium or hospital would be shortened. It is cheaper for any community to establish "artificial pneumothorax" clinics than to maintain patients over long periods of time in sanatoriums.

The group of workers who are already advocating the extension of artificial-pneumothorax treatment to earlier cases is constantly growing

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[2] Read in part before the Milwaukee Pediatric Society, October 12, the Wisconsin 7th District Medical Society, LaCrosse, November 8, and the Columbus, Ohio, Academy of Medicine, November 13, 1933.

larger. In another paper (4) we have called attention to the great value of artificial pneumothorax in the treatment of tuberculosis and have shown that it is now a standard method of treatment; that it inhibits the proliferation of tubercle bacilli in tuberculous lesions, and stimulates the formation of fibrous tissue; that it does no harm to the healthy lung tissue and that it has no bad effect upon the heart or other parts of the body. Attention was also called to the complications which may accompany artificial-pneumothorax treatment but those of a serious nature occur so rarely as to be of insignificance when artificial pneumothorax is indicated in any case of pulmonary tuberculosis. Moreover, it was shown that while good results have been accomplished for a certain group of patients a far larger group have not been benefited materially because their disease was of too long standing or too extensive when an attempt was made to institute the treatment.

In 1915, Woodcock (5) said: "There are dangers in connection with the production of artificial pneumothorax but the greatest—and about this let there be no mistake—is the neglect of it." Three years later, Greer (6) advocated the use of artificial pneumothorax in all unilateral first-stage cases, and stated that the time is not far distant when this procedure will be more generally practised.

In 1919, Gamero and Cerdeiras (7) argued strongly for the early administration of artificial pneumothorax in pulmonary tuberculosis. They were of the firm opinion that delay had materially hampered the progress of this valuable method of treatment and brought undeserved discredit on it.

Ebert (8), in 1922, said that artificial pneumothorax should be extended so as to include many of the milder cases. He stated that a large number of patients who with other methods would require a long course of treatment can be advantageously treated by artificial pneumothorax.

In 1923, Crocket (9) said:

> In conclusion, I would emphasize that this excellent curative measure should not be reserved for advanced and hopeless types of the disease only. It is safe. It can be attempted more often, and it will prove more frequently effectual in early cases. Its rationale is sound and scientific, and by securing fibrosis in and around the diseased area, it is more likely to produce perfect permanent results than any other method at present practiced by the profession.

In 1924, Fine (10) advocated the use of partial artificial pneumothorax in early tuberculosis. The same year, Davies (11) said:

Surgical interference is not, therefore, a necessity; on the other hand, the greater my experience the more emphatic do I become in my assertion made first some years ago now, that no case of pulmonary tuberculosis which has been diagnosed with certainty is too early a one for treatment by artificial pneumothorax, provided there are no contraindications. I have never regretted doing an artificial pneumothorax in an early case, but I have often regretted not doing one.

The same year, also, Bendove (12) and H. B. Shaw (13) advocated collapse in selected cases of minimal tuberculosis. Shaw says it seems advisable not to postpone the induction of pneumothorax while giving other means a trial. At the same time, Deuel (14) stated that pneumothorax is best indicated in cases with spreading tuberculosis, that has not reached the pleura or has not developed cavitation, since in such cases complications are much less common and the opposite side is not so badly diseased as in the more advanced conditions. In 1925, Singer (15) reported 5 minimal cases treated by artificial pneumothorax, of whom four became apparently well and only one remained unimproved. The same year, Bronfin, Nelson and Zarit (16) arrived at the following conclusions:

The weakest point in the present-day practice of artificial pneumothorax is its late application. The longer the duration of the pulmonary lesion, the greater the tendency to unsatisfactory mechanical results. The incidence of complications, such as effusions and pulmonary perforations, is greater in the advanced than in early cases. The chances for economic or actual recovery are better when pneumothorax is instituted comparatively early in the disease.

Beeh (17) has called attention to the fact that artificial pneumothorax became much more extensively used between 1919 and 1929 and also to the increase in its use in early cases. In 1933, Cedric Shaw (18) reported the results of artificial-pneumothorax treatment in 267 cases. He says: "Because an analysis of the cases shows clearly that the mortality varies directly, and the ultimate working capacity and residual symptoms inversely, with the degree and severity of disease at the inception of treatment, it is suggested that a pneumothorax should be induced, in an earlier type of case than the conventional." Burrell (19) states that inasmuch as artificial pneumothorax has saved many lives, it is reasonable to assume that it would save many more if it were employed in the earliest stage of tuberculosis before adhesions have formed and while the disease is unilateral. Fischel (20) says: "Since we had the occasion to observe

cases of early infiltrations, we have made use of surgical collapse at an early date, whenever the tendency to progression was noticed, and although the time is too short to give, at present, a conclusive report, we should like to say that the results are so far very encouraging."

Ulrici (21) finds that satisfactory results have definitely increased in his experience. For example, from 1918 to 1921, 18 per cent were satisfactory, while from 1926 to 1928 the percentage had increased to 47, by the greater use of pneumothorax. Of all the patients who showed good results two to five years after treatment, 61 per cent did not have exacerbations after nine to twelve years. Of all the groups treated, he finds that permanent results, that is good health for ten years, are obtained in 28 per cent of unilateral pneumothorax cases. He is of the opinion that these results can be greatly improved if collapse therapy can be started earlier in the disease in a larger number of patients. He believes the duration of treatment is a very important factor. Of the patients he treated for more than two years, 68 per cent showed permanent results, while, in those treated six months or less, only 9 per cent showed permanent results. Ulrici says the results of collapse therapy will be improved by earlier diagnosis and earlier operation, and prolonged treatment. In 1927, Pissavy, Bernard and Rist (22) reported the results of their pneumothorax work, when Pissavy pointed out that at the end of four years about 50 per cent of his patients were dead. He was of the opinion that fewer complications would occur if the pneumothorax was instituted earlier. Bernard reported complete cure in 24 per cent of his total group, but when he divided them into two groups, the first consisting of those who had advanced lesions, and the second those with active early lesions when pneumothorax was instituted, he found that 55 per cent of the latter group were cured. Rist found that after a period of six years, 38 per cent of his patients treated by artificial pneumothorax had died, whereas 90 per cent of patients untreated by pneumothorax were dead. Stallings (23) says there is no question in the minds of physicians whoare in this work that an increase in the number of cases recovered will be noted in the next few years as the doctors throughout the country become more familiar with this treatment and advise its use more often. Naive (24) says artificial pneumothorax would be of value and should be used in many more cases than those in which it has been applied and since so much depends upon a complete collapse it should be used earlier in the course of the disease.

O'Brien (25) is of the opinion that there can be two reasons for not

immediately instituting some form of surgical collapse. One is that the lesion is so small as to make one optimistic enough to depend on bed-rest alone; the other reason is that the disease is so advanced that collapse therapy would not help. Knüsli (26) in discussing the treatment of children and young adults states that an early institution of collapse therapy is essential. Fechter (27) called attention to the fact that when collapse therapy is immediately instituted, the necessary duration of the treatment can be definitely shortened. Jessen (28) finds that the early cavity cases treated by artificial pneumothorax yield the best results. Lassen (29) reports 40 cases with early infiltrations, who were under observation two years later. Twenty-seven were able to work, five to do part time work, four unable to work, two died, and two could not be traced. Thus 80 per cent had been restored to part- or full-time working capacity. This is in quite sharp contrast to the reports of so many authors who began artificial pneumothorax late. This form of treatment, when instituted early, very quickly restores the ability to work which is an important item in the lives of most patients.

Hawes and Stone (30) speak of collapse therapy as one of the most effective means of treating tuberculosis, in that it prolongs life, reduces mortality from disease, and shortens what would otherwise be a long period of invalidism, and of even greater importance hastens the patient's return to industry. They lament the fact that the procedure is not used far more extensively. They say,

> The medical profession seems to hold aloof from these procedures and to look on them rather as measures of last resort. Compare pneumothorax in tuberculosis, for instance, as the most common and certainly the simplest means of putting the lung at rest, with insulin in diabetes and with liver and liver extracts in the primary anemias. Physicians are perfectly well aware of the great good that the latter two can accomplish. Yet, for the obvious reason that for every case of diabetes or primary anemia there are hundreds of cases of pulmonary tuberculosis, the total of good that can be done by the former fades into insignificance when compared with what can and should be done by collapse therapy in tuberculosis when in suitable hands and in properly selected cases. We do not mean to imply that the medical profession is ignorant of the various methods of putting the lung at rest. It is probably because the average physician has no experience in such procedures and is not equipped to carry out these methods of treatment that he is loath to recommend them to his patients. The reaction of many physicians, when the consultant suggests that pneumothorax is indicated, is too apt to be, "Oh, no, Doctor, she hasn't reached

that stage yet." In our own practice this has been only too frequent an occurrence. Thus the patient and the family are persuaded against it and much precious time is lost while the disease attacks the other lung, after which all possibility of putting one lung at rest is gone forever. The same point of view is apt to be found in many tuberculosis hospitals and sanatoriums.

Again they say,

In our own work we have little or no difficulty in persuading a patient that pneumothorax should be tried, although it often takes time, patience and tact. On the whole, we believe that the vast majority of physicians are not aware of the almost miraculous results that can be accomplished by this means even under the most discouraging and hopeless conditions. The general practitioner is well able to handle his anemia patients with liver and liver extracts and his diabetic patients with insulin. But because few practitioners are equipped to handle pneumothorax cases, they rarely recommend it. Thus the opportunity is lost.

Hawes and Stone (30) after consulting numerous authorities found that, with one or two exceptions, the majority were of the opinion that collapse therapy in some form should be used far more frequently than it is. Those whom they consulted varied in their opinions as to the number of patients they saw eligible for collapse from 15 to 17 per cent. Of course, these persons were from tuberculosis centres where very modern methods are employed. Hawes and Stone lament the fact that in the New England States only 4.2 per cent of the cases of tuberculosis are receiving collapse therapy.

Leslie (31) says, "Saving the overwhelming and rapidly fatal infections, there are few cases that are not suitable for some form of collapse therapy while still in the unilateral stage of involvement; a patient should receive it rather than merely being assigned to bed." Head and Schlack (32) state that for the past eighteen months they have proceeded upon the principle that every case of unilateral pulmonary tuberculosis should be treated by some form of collapse therapy. Hruby (33) says: "Indications for collapse therapy are widening as our knowledge increases and as our technic improves. We are, today, instituting collapse therapy in cases which would have been considered definitely unsuitable some years back. The number of cases brought within the scope of collapse therapy is ever on the increase." Tice (34) says: "Abroad, particularly, the beneficient influence of pneumothorax therapy in the early case is being widely heralded. Many, today, are unwilling to wait for extensive,

unilateral disease. They are rather inclined to give the early case with progressive tendency the advantages of a period of compression therapy. This is particularly true in the case of the patient with a positive sputum."

Thus the reports come both from institutional workers and private practitioners and the results are similar. The accomplishments are marvelous when one considers the stage of disease, but they do not begin to represent the potentialities of the treatment. In reading dozens of articles on the subject, the recurring thought has been that treatment was instituted too late. The writers report cavities unclosed and adhesions making collapse impossible. Certainly, treatment instituted at an earlier stage would have prevented many of these unfavorable conditions.

We are reminded of a discussion between an orthopaedist and a heliotherapist concerning the treatment of tuberculosis of the bones and joints. It was at the time when the pendulum had swung far over on the side of heliotherapy and the physician representing this school stated that within five to seven years many cases of bone and joint tuberculosis can be well under control. The orthopaedist called attention to the time element by stating that if the patient's time was worth nothing and neither his nor the taxpayers' money was valuable, perhaps he would be justified in devoting five to seven years to the treatment; but since the time of the patients who employed him was very valuable he was impelled to operate when indicated and restore them to a working capacity within a few months rather than five to seven years.

Bethune (35) speaks of the patient who can afford the time and the money to carry on for an indefinite period with the assurance of complete restoration of health at the end of several years of bed-rest. It would seem like a waste of both time and money to carry on under these circumstances when a more specific and much quicker method of treatment is available.

Leslie (31) writes of rest as the most effective treatment available for pulmonary tuberculosis and is of the opinion that it should be administered in the early stages of the disease. He calls attention to the fact that collapse therapy results in intensive rest that is impossible to obtain from bed-rest alone. He says, "This specifically localized rest, with its collateral favorable effect of relaxation or compression of the infiltrated or cavernous lung, offers many tuberculous patients such a vastly improved prognosis that collapse therapy is considered by the majority of expert phthisiotherapists to have created a revolution in the treatment of pulmonary tuberculosis."

One very definite indication in minimal lesions is that the disease be of the reinfection type. We have come to appreciate the fact that there are two types of tuberculosis which appear in the chest and the treatment of one is not the treatment of the other. The body reacts so differently to these two types that they may be looked upon as almost two entirely different disease entities. The first-infection type of tuberculosis, commonly known in this country as the childhood type, is, in the majority of cases, brought well under control by the natural resisting forces of the body unaided. Such tuberculous lesions, even though they may appear rather extensive in the lung parenchyma, usually require no treatment except that included in well-regulated living, which should be prescribed for any child or adult in good health. This type of disease now frequently occurs in young adults.

The reinfection type, often spoken of as the adult type of tuberculosis, presents quite a different picture. It is the type, which if allowed to progress, causes symptoms, physical signs and, in fact, illness and death. It is always preceded by the first-infection type and may appear at any age period of life, even in infancy, after the first-infection type has been well established and the tissues have become allergic. It is the type of disease which often requires treatment. Therefore, before treatment is prescribed or prognosis is rendered one should attempt to determine whether one is dealing with the first-infection type or the reinfection type of tuberculosis. This determination would never be difficult if we had records of all human beings such as those Sir Robert Philip (36) keeps of the members of his clientele; that is, if we knew when the individual in question first reacted positively to tuberculin our difficulties would be solved in most cases, as far as type determination is concerned. If the tuberculin test has always been negative, and very recently has become positive and in a few weeks or months a lesion appears in the lung, in all probability it is of the childhood type. Such a lesion should be kept under close observation but one should refrain from instituting drastic treatment or rendering a bad prognosis unless subsequent developments warrant them. The individual who has reacted positively to tuberculin over a long period of time with no demonstrable lesion, but who later develops a tuberculous lesion, in all probability has the reinfection type of disease.

Fortunately, many persons have the ability to control unaided minimal lesions of the reinfection or adult type. However, enough of them continue to progress, so as to justify the closest possible observation from

the time they are first detected. They may appear to remain unchanged for months or years and then increase in extent. On the other hand, they may continue to increase in extent from the time they are first detected. Those which are not increasing in extent, are not breaking down, are not discharging tubercle bacilli, etc., do not need hospitalization or any drastic form of treatment; well-regulated living suffices, provided they are kept under close observation. But those minimal lesions which are progressive, even though they are causing no symptoms, no abnormal signs and tubercle bacilli cannot be demonstrated in the sputum, should be treated drastically,

Strict bed-rest fails sufficiently often in such cases as to make us feel that this treatment alone is not dependable. Rest in bed provides for some reduction of the activity of the diseased lung but perhaps not enough to be of great significance. The general building up of the body resulting from strict bed-rest was for a long time thought to be extremely valuable in providing increased resistance to disease. Perhaps it does, but it is not an uncommon experience to see tuberculous disease increase in the presence of marked improvement of the general bodily condition. In fact, those who have observed their patients treated by bed-rest alone over months and years have often seen the disease, even though minimal in the beginning, go through periods of remissions and exacerbations, and in a considerable percentage the disease ultimately became advanced and all too often, when the artificial pneumothorax was thought to be indicated, lesions had made their appearance in the opposite lung; cavities had formed and adhesions were present. Cedric Shaw (18) made a study of 267 cases treated by artificial pneumothorax during 1922–1932 and compared the findings with those of Bardswell and Thompson (37), whose patients were treated by sanatorium routine alone. Among the early cases treated by pneumothorax, there was no mortality as opposed to 23.1 per cent mortality for males and 13.5 per cent for females among the sanatorium cases; in the moderately advanced cases, the mortality was slightly more than 10 per cent for both males and females in the artificial-pneumothorax group, as opposed to 45.3 per cent for males and 42.7 per cent for females in the sanatorium group; in the far-advanced cases, the mortality in the pneumothorax group was 46.9 per cent and 48 per cent for males and females respectively, as against 74.4 per cent and 67.6 per cent for males and females respectively in the sanatorium group.

Leslie (31) says,

While conceding the immense value of unaided bed rest, this does not seem to be a method of attack but rather a method of passive resistance. There is surely preponderating evidence in favor of the early application of collapse therapy, when statistical studies prove its value, from the standpoint both of shorter hospitalization and more permanent future protection for those patients who tend to improve with bed rest alone, and of its immediate beneficial effect for those patients who do not show this tendency.

Minnig (38) says: "If there is the slightest doubt as to whether the patient is going to get well with the ordinary methods of treatment he should be given artificial pneumothorax at once, because the formation of adhesions is the one insurmountable barrier, and can be overcome only by giving the gas earlier in the game."

The question arises as to whether procrastination is ever justified. If collapse therapy is good for a case of advanced pulmonary tuberculosis, would it not be better for one with minimal progressive disease? Before our eyes is a lesson from the surgeons. The appendix often became diseased before the days of abdominal surgery. In some patients, good recovery was experienced; in others, rupture of the diseased appendix led to peritonitis. After a severe illness some recovered but many died. This is about where we were in the treatment of pulmonary tuberculosis before the days of collapse therapy. In the early days of abdominal surgery, appendicectomy was not practised except in the severe cases. Often by the time laparotomy was performed the appendix had already ruptured and peritonitis was well developed. Obviously the surgical risk was not good and, as earlier diagnosis became possible, the surgeon learned that he could materially improve the surgical risk by removing the diseased organ before serious complications developed. Therefore, he no longer waits until the appendix is ready to rupture or has ruptured before he operates. Moreover, his patient avoids a long period of convalescence in a hospital; in fact, this period has been reduced to a few days.

There is no more reason why we should wait to institute collapse therapy until the disease has become extensive and the risk poor than there is for the surgeon to wait until the appendix has ruptured before he operates. There are two chief dangers from procrastination in progressive minimal pulmonary tuberculosis. The first danger is to the patient himself. The more the disease spreads the more destruction of lung tissue will result and the more likely he is to become definitely ill from it. Cavities form, and the lung often becomes adherent to the chest-wall. In other words, the patient's chances of complete recovery are gradually

vanishing. The second danger is to his associates. He has a communicable disease and if it is allowed to progress, sooner or later tubercle bacilli appear in the sputum and will be disseminated to others. If one acts quickly in the institution of collapse therapy extension of the disease may be prevented, so that the patient never actually becomes ill and if the sputum is negative it will probably remain so, whereas if it has already become positive it may be rendered negative. Thus, the two chief dangers, one to the patient and the other to his associates, have been reduced materially. The following cases illustrate the dangers of procrastination.

In June 1927, a young man of twenty-four years, because of exposure to a friend who had tuberculosis, requested an examination. There were no symptoms and the physical examination was entirely negative. The X-ray film, however, showed a minimal lesion on the right side at the level of the 2nd rib. This did not appear to change during the next few months. This young man entered his profession and worked until April 1931, when he had a frank pulmonary haemorrhage. He later reported for an examination which showed considerable extension of the disease with cavity-formation. Artificial pneumothorax was recommended but because of business affairs he continued with his work and treatment was not instituted until July 3, 1931. He took a vacation of three months during most of which time he remained in bed. In October 1931, he returned to his profession and has continued at work.

Another patient reported for examination on May 12, 1923. Three days before he had had a diagnosis of tuberculosis involving the left upper lobe with tubercle bacilli in his sputum. He had slight cough and expectoration; had lost about 10 lbs. the previous six months; his temperature ranged from 99° to 100.4° and he had a slight haemorrhage on May 8, 1923. Moderately coarse râles were elicited anteriorly above the 2nd interspace. X-ray films showed parenchymal infiltration over this area. The patient was placed on strict bed-rest in the home, where his symptoms subsided and disappeared, and his physical signs decreased. After approximately six months, graduated exercise was begun. He remained free from symptoms until November, 1926. At that time the disease showed definite extension and artificial pneumothorax was instituted one month later. He returned to work in March, 1927, and has continued to the present time. Such cases lead one to feel that a great deal of time is often lost by overconservatism. One is convinced that it would have been far better to have instituted collapse therapy in this case in 1923.

A third patient reported on July 21, 1926, for an examination because of a slight cough and a sense of fatigue during the preceding three weeks. She had also

lost 3 or 4 lbs. in weight. The X-ray film revealed a small localized area of infiltration in the right upper lobe. The patient was advised to return in six weeks for further examination. During the latter part of the summer, however, her symptoms disappeared, and she did not report for reëxamination until November 24, 1926, following a pulmonary haemorrhage. Examination of the chest revealed extension of the tuberculous infiltration in the right upper lobe. She returned to her home and was on a strict regimen of her family physician until June 17, 1927, when there was evidence of cavity-formation in the right upper lobe. Artificial pneumothorax was later instituted but could not be carried out successfully because of adhesions.

In each of these cases, artificial pneumothorax instituted earlier probably would have prevented the destruction of considerable areas of tissue, preserved working capacity, and prevented the spread of tubercle bacilli to the patients' associates. Many other similar cases could be cited. Although bed-rest alone suffices in some minimal cases, all too often we see those who have been on bed-rest a year or longer in institutions or homes, return months or years later with reactivation and extension of their disease.

In the past, minimal tuberculosis of the adult type has been diagnosed relatively rarely. Leslie (31) points to a very significant fact with regard to the diagnosis of tuberculosis, in that such a small percentage of cases are in the minimal stage. He found in the Michigan State Sanatorium, 5.5 per cent minimal, 28.2 per cent moderately advanced, and 66.3 per cent far-advanced cases.

Indeed, in the past approximately 80 per cent of the patients admitted to our institutions for the treatment of tuberculosis had more than minimal disease on admission. A considerable percentage of the remaining 20 per cent had the first-infection type only, which should not require institutionalization, or nonprogressive adult types of lesions, or did not have tuberculosis. Therefore, the sanatorium workers of the country have had very little opportunity to deal with the adult type of tuberculosis in a stage when treatment is so easily administered with such excellent results. The most of their time has been spent in dealing with patients whose best chances of recovery had vanished before admission to institutions and who, if they lived, required long periods of bed-rest, whether or not collapse therapy was instituted. Their present attitude toward the treatment of tuberculosis, by reason of their experience, must, therefore, be that which is often necessary for the moderately and far-advanced case. This is a regrettable situation, inasmuch as they have

received undue blame for the long and expensive periods of hospitalization and the tremendously high mortality from tuberculosis among patients in their institutions or soon after discharge. The only way the situation can ever be changed and conditions improved is through a method of seeking tuberculosis in the various communities, just as the veterinarians do with animal herds, and finding the disease months or even years before it would cause symptoms sufficient to bring patients for examination. When this is done and the minimal cases properly treated, the two dangers from adult minimal tuberculosis, extension of disease and dissemination of tubercle bacilli, will be removed from the individuals and their associates. When that time arrives, collapse therapy will play an extremely important rôle in tuberculosis control.

But is it necessary to place every patient with the reinfection type of pulmonary tuberculosis, whether minimal, moderately advanced or even far advanced, in an institution, public or private, while collapse therapy is being instituted and continued? Is it even necessary to make each one a strict bed-patient at home? There is a great demand for beds in tax-supported institutions for patients suffering from extensive tuberculosis. These institutions have always done their greatest good by accepting such patients, making them comfortable, and keeping them isolated so they will not spread bacilli to persons outside the institution. We are anticipating in the future the detection of far more minimal and early moderately advanced cases of tuberculosis through modern case-finding methods. If a considerable number of these cases are to be treated for months and years in our institutions, it means that these institutions must be definitely expanded or the activities which have resulted in the greatest good must be reduced. Already taxpayers are beginning to chafe under the burden of such institutions in some states. Instead of discussing the possibilities of increasing their facilities, definite reductions in appropriations are being made and some institutions are threatened with abolishment.

Artificial pneumothorax in progressive minimal and some advanced cases may be carried on with great success in the home. Hruby (33) says:

> For the most part, pneumothorax therapy is currently regarded as a sanatorium procedure. In most quarters, it is believed that a program of lung collapse in field practice is inadmissible. It is considered, indeed, that such a program constitutes a new departure, perhaps a radical innovation. This, however, is

not the case. Various programs of field pneumothorax have been organized in the past and, in fact, many such programs are at present in operation particularly in Europe. Pneumothorax in the field or in the home is no new thought. .... Today we are drifting away from the tendency to keep the patient in residence in the sanatorium or hospital over comparatively long periods of time.

Cedric Shaw (18) reports observations on 184 cases that went to a sanatorium after the induction of artificial pneumothorax and 83 others treated by artificial pneumothorax alone. The percentage mortality among the minimal and far-advanced groups is almost identical, but in the moderately advanced group those treated by artificial pneumothorax alone showed a slightly higher mortality. He says: "As to the working capacity and the residual symptoms of the survivors, the differences between the two classes are insignificant." Tice (39) says:

France has awakened to the potentialities of pneumothorax therapy in the field on a widespread scale. It has been proposed that legislation be passed providing that collapse therapy be made available to every suitable case needing such treatment throughout France. This is, indeed, a far-sighted proposition, and if it becomes operative will undoubtedly wield an immense influence in preventing infection and reducing morbidity—in other words, in the social rehabilitation of the tuberculous patient.

Cutler (40) reports 111 cases on ambulatory therapeutic pneumothorax over a period of three and one-half years, and states that his results compare favorably with those obtained in most sanatoria handling the same type of patient. He estimates that there are approximately 828,000 persons with pulmonary tuberculosis in this country and that 400,000 of them could be satisfactorily treated by ambulatory pneumothorax.

Edwards (41) has called attention to the fact that pneumothorax patients may be treated by their private practitioners. Greer (6), as early as 1919, reported his observations in private practice and called attention to the fact that for many such patients the sanatorium is not necessary. Poix and Bosnieres (42) have described their method of treatment of tuberculosis by pneumothorax so that hospital residence is not necessary. They made a study of the results obtained in 47 cases in which the patients were not hospitalized and compared them with 124 hospital cases. They observed no superiority in the results gained by hospitalization. Markey (43) says that "home" cases may report to the physician's office or local hospital for refills after the third or fourth. H.

Batty Shaw (44) says that the artificial pneumothorax treatment is so far superior to the sanatorium treatment of tuberculosis of the lungs that the former should become the treatment of choice.

The evidence is proving quite conclusively that many patients with progressive minimal adult-type pulmonary tuberculosis, and even some with advanced disease, may be treated very successfully by artificial pneumothorax with only a short period of bed-rest in the home or a local hospital while the treatment is being instituted. At the same time, there is a gradually increasing number of vacant beds in our private hospitals which may be used to great advantage for such patients. In fact, such hospitals are becoming more and more popular among physicians who treat tuberculosis in private practice.

Another problem arises among persons with no symptoms, who are found to have progressive adult-type pulmonary tuberculosis in the minimal stage. It is the problem of convincing the patient that he needs a long period of hospital treatment. Many patients who cannot possibly be convinced that such treatment is necessary will submit to brief periods of bed-rest in local hospitals or in homes while artificial pneumothorax is being established if the physician feels such bed-rest is necessary.

Another section of the group who refuse hospitalization will submit to artificial pneumothorax provided they can continue in their regular activities. Artificial-pneumothorax treatment has even been extended to the ambulatory case that takes a brief or no period of bed-rest. Burrell (45) calls attention to the fact that many patients are unable to give sufficient time to sanatorium or other treatment which will keep them away from work. He points out further that the treatment does not necessarily interfere with work in all cases and, therefore, it is unusually valuable among industrial workers. Kogan (46) reported 33 such cases, and found no less favorable results than among those who had had sanatorium treatment. Blumel (47), Pick (48), Vôute (49), Apel (50), Mende (51), Fernandez (52), and others have discussed ambulatory artificial-pneumothorax treatment during the past decade. This subject with a report of a group of patients and a brief discussion of some of the literature was presented in a previous article (53).

In the past, most cases of tuberculosis reached the moderately or far-advanced stage before their disease was diagnosed or while under observation. In the occasional case seen while the disease was minimal, artificial pneumothorax was usually thought to be contraindicated. Therefore, very few reports on artificial-pneumothorax work contain many cases

treated in the minimal stage. However, with our modern diagnostic methods, a much larger number of cases are being detected while in the minimal stage. By the more extensive use of these methods, we may hope to arrive at a time when the majority of cases of clinical tuberculosis will be detected before symptoms make their appearance. Through observations made at the Lymanhurst School for Tuberculous Children, the University of Minnesota Health Service, and elsewhere, we have been convinced that every progressive case of minimal tuberculosis of the reinfection type should be treated by artificial pneumothorax.

In table 1 is listed a group of 52 cases so treated. Only 2 cases were treated by this method before 1926, one of whom lost her collapse through the development of obliterative adhesions five months after the treatment was instituted. She continued on institutional treatment for four years. She has since graduated from high-school and is now in the University, and all that remains on the X-ray film is shadows interpreted as calcium deposits and fibrous strands. Here it is difficult to determine how much effect the artificial pneumothorax had on the healing of her disease, since it was continued over a brief period of time and she remained in bed for years after it was instituted.

Another similar case is patient 6, who had artificial pneumothorax instituted in the winter of 1927. Her lesion was in the right apex. She remained on treatment only four months when another physician advised against its continuation on the ground that the disease was minimal. She received institutional care until February 12, 1929. She now has two deposits of calcium in the right apex. In our opinion two of these cases had only the first-infection type of tuberculosis and would have recovered without artificial pneumothorax or institutional care.

Case 13 had a basal lesion and only a partial collapse. The air-pocket was in the anterior part of the pleural cavity and admitted only about 200 cc. of air at each treatment. Because of the lung markings posteriorly to it, this pocket was not easily visualized except by rotating the patient on the fluoroscopic examination and making films in special position. She consulted another physician for a gastrointestinal disturbance, who in addition to the abdominal examination made an anteroposterior film of her chest. He stated that he was unable to visualize an air-pocket, which convinced her that she was not receiving artificial-pneumothorax treatment. This resulted in loss of confidence and she discontinued the treatments. However, she has remained in good health as far as the lung condition is concerned.

TABLE 1

CASE NUMBER	OCCUPATION	UNILATERAL OR BILATERAL	DATE OF FIRST TREATMENT	AGE WHEN INSTITUTED	GOOD COLLAPSE	DISCONTINUED TREATMENT	PERIOD OF BED-REST	REMARKS
1	Student	Unilateral	October, 1922	23	Yes	March, 1923	4 years	Usual activities
2	Clerk	Unilateral	July, 1924	26	Yes	No	2 months	Usual activities
3	Teacher	Unilateral	June, 1926	25	Yes	October, 1931	None	Usual activities
4	Teacher	Unilateral	October, 1926	22	Yes	December, 1927	6 weeks	Married; 2 children; usual home activities
5	Nurse	Unilateral	January, 1927	22	Yes	May, 1928	None	Married; 1 child; usual home activities
6	Nurse	Unilateral	March, 1927	25	Yes	July, 1927	6 months	Usual activities
7	Nurse	Unilateral	April, 1927	25	Yes	April, 1931	14 months	Usual activities
8	Student	Unilateral	April, 1927	24	Yes	No	18 months	Usual activities
9	Nurse	Unilateral	June, 1927	27	Yes	April, 1933	1 year	Few adhesions; disease in contralateral lung; empyema
10	Student	Unilateral	June, 1927	16	Yes	October, 1928	2 months	Usual activities; accidental death, autumn of 1934
11	Telephone operator	Unilateral	July, 1927	23	Yes	December, 1928	7 months	Usual activities
12	Clerk	Unilateral	March, 1928	22	Yes	No	6 months	Usual activities
13	Housewife	Unilateral	April, 1928	25	Fair	April, 1931	2 months	Usual activities
14	Clerk	Unilateral	October, 1928	18	Yes	No	7 months	Usual activities
15	Office boy	Unilateral	April, 1929	18	Yes	April, 1929	8 days	Died April, 1929, of miliary tuberculosis
16	Nurse	Unilateral	May, 1929	38	Yes	No	3 months	Usual activities
17	Stenographer	Unilateral	June, 1929	35	Yes	No	None	Usual activities
18	Cashier	Unilateral	December, 1929 (left) June, 1931 (right)	22	Yes	No	6 months	Tuberculous pneumonia contralateral lung; left allowed to re-expand; right collapsed
19	Office manager	Unilateral	January, 1930	29	Yes	No	6 months	Usual activities

20	Housewife	Unilateral	1930 (diagnostic pneumothorax (left)) May, 1933 (right)	29	No	No	1 month	Usual activities
21	Student	Unilateral	June, 1930	17	Yes	January, 1933	7 months	Usual activities until death from pneumonia, January, 1933
22	Housewife	Unilateral	July, 1930	29	Yes	June, 1931	2 months	Usual activities
23	Student	Unilateral	September, 1930 (right) October, 1931 (left)	16	Yes	No	6 months	Disease spread to opposite side; usual activities
24	Clerk	Unilateral	November, 1930	22	Yes	No	1 month	Usual activities
25	Clerk	Unilateral	January, 1931	22	Yes	No	1 month	Usual activities
26	Nurse	Unilateral	March, 1931	31	Yes		22 months	Later developed peritonitis; doing well
27	Nurse	Unilateral	March, 1931	28	Yes	No	None	Usual activities
28	Student	Unilateral	May, 1931	15	Yes	No	3 weeks	Usual activities
29	Student	Unilateral	August, 1931	22	Yes	No	6 months	Usual activities
30	Student	Unilateral	August, 1931	16	Yes	No	3 weeks	Usual activities
31	Salesman	Unilateral	October, 1931	25	Yes	No	None	Large serous effusion; usual activities
32	Housewife	Unilateral	December, 1931	27	Yes	No	23 months	Still in institution
33	Nurse	Unilateral	February, 1932	26	Yes	August, 1934	None	Usual activities
34	Housewife	Unilateral	February, 1932	37	Yes	August, 1933	3 months	Good condition
35	Student	Unilateral	February, 1932	16	Yes	No	2 weeks	Usual activities
36	Housewife	Unilateral	April, 1932	30	Yes	June, 1932	7 months	Usual activities
37	Student	Unilateral	May, 1932	10	No	No	6 months	Usual activities
38	Student	Unilateral	May, 1932	16	Yes	No	2 weeks	Usual activities
39	Student	Bilateral	June, 1932	10	Yes	June, 1934	None	Usual activities
40	Student	Bilateral	December, 1932 (left) July, 1933 (right)	16	Yes	No	9 months	Died of multiple tuberculosis, March, 1934
41	Student	Unilateral	December, 1932	17	Yes	No	5 months	In institution until October, 1933. Spread of disease to opposite side; now bilateral pneumothorax in institution

TABLE 1—*Concluded*

CASE NUMBER	OCCUPATION	UNILATERAL OR BILATERAL	DATE OF FIRST TREATMENT	AGE WHEN INSTITUTED	GOOD COLLAPSE	DISCONTINUED TREATMENT	PERIOD OF BED-REST	REMARKS
42	Housekeeper	Unilateral	April, 1933	28	Yes	No	1 month	Usual activities
43	Student	Unilateral	May, 1933	19	Yes	No	3 months	Usual activities
44	Student	Unilateral	July, 1933	20	Yes	No	None	Usual activities
45	Nurse	Unilateral	September, 1933	28	Yes	No	None	Usual activities
46	Nurse	Unilateral	October, 1933	24	Yes	No	4 weeks	Large serous effusion; usual activities
47	Clerk	Unilateral	November, 1933	18	Yes	No	None	Usual activities
48	Housekeeper	Unilateral	January, 1934	37	Yes	No	1 week	Usual activities
49	Stenographer	Unilateral	April, 1934	27	Yes	No	None	Usual activities
50	Student nurse	Unilateral	May, 1934	20	Yes	No	6 weeks	Usual activities
51	Student	Unilateral	June, 1934	15	Yes	No	None	Usual activities
52	Clerk	Unilateral	July, 1934	27	Yes	No	None	Usual activities

Case 15 has unilateral disease which had been shown by his family physician to be progressing. The X-ray films before artificial pneumothorax was instituted showed no evidence of miliary tuberculosis, nor did he have any symptoms of this form of the disease. However, eight days after artificial pneumothorax was instituted he died of miliary tuberculosis. Although the pleural space was shown to be free, the collapse was not complete because of the small amount of air introduced on the original treatment and the one refill. We have never felt that the artificial pneumothorax had anything to do with the development of miliary tuberculosis in this case.

Case 21 was a school-girl who had a minimal but definitely progressive lesion causing mild symptoms. She was placed in an institution where artificial pneumothorax was instituted. Symptoms disappeared, but she remained in an institution for twenty-two months. She was then discharged, returned to her home and was leading a normal life, when in the winter of 1933 she developed acute nontuberculous pneumonia and died in a few days.

Case 9 was on strict bed-rest for one year after artificial pneumothorax was instituted. All symptoms disappeared and her general condition was excellent. At the end of a year, she was given graduated exercise and in due time returned to work. The pneumothorax was continued. There was a small, apparently fibroid lesion in the extreme apex of the contralateral lung which at times showed evidence of slight progression. In March, 1933, she had a pulmonary haemorrhage, which apparently was from the lesion in the contralateral lung. In a few days she was suffering from pneumonia, apparently caused by the blood aspirated into the base of this lung. Soon after she recovered from the pneumonia, purulent fluid appeared in the pneumothorax cavity. This was found to contain staphylococci and later a fistula through the visceral pleura was detected. She was immediately institutionalized.

Case 18 remained on strict bed-rest for six months after artificial pneumothorax was instituted for a minimal basal lesion, which had caused haemorrhage. She responded splendidly and after a period of graduated exercise she became quite active. On March 6, 1931, she had a profuse haemorrhage. Whether this was from the partially collapsed lung, we could not be certain. However, she was found to have tuberculous pneumonia in the base of the contralateral lung and we were inclined to believe that the haemorrhage was from this lesion. The left lung was allowed to reëxpand and, after the acute symptoms had subsided, artificial pneumothorax was instituted on the right side on June 16, 1931. She was kept on strict bed-rest following this. She again responded splendidly and the lesion in the left lung appeared very fibrotic. She is still in an institution and her general condition is excellent.

Case 23 had a minimal lesion in the right upper lobe. She responded well to artificial-pneumothorax treatment and remained in bed for six months. She was then placed on graduated exercise. Approximately a year after pneumothorax was instituted a lesion made its appearance in the contralateral lung.

It definitely progressed and bilateral artificial pneumothorax was instituted. This brought all symptoms under control, but the pneumothorax on the right side was lost on May 20, 1933, through obliterative adhesions. The pneumothorax on the left side is being continued and she works on a part-time basis whenever a position is available.

Case 36 had a minimal lesion in the left lung in addition to pleurisy with effusion. The fluid was removed and air was introduced. She was later admitted to an institution where the lung was allowed to reëxpand. She has since returned to her home where she is leading a fairly normal life.

Case 40 had bilateral disease with the more extensive lesion on the left side. Partial artificial pneumothorax was instituted in December 1932. She did splendidly until June 1933 when she had a frank pulmonary haemorrhage, apparently from the lesion in the right lung. This was followed by definite extension of the apical lesion and pneumonia in the right base. Partial artificial pneumothorax was instituted on the right side July 5, 1933. She later died of multiple tuberculous lesions.

Case 20 was found to have a small basal lesion on the left side in 1930. Its appearance was such that we could not be certain of the diagnosis. Diagnostic artificial pneumothorax was performed but this did not aid materially. The lesion has been closely observed but has undergone no change as far as we can determine by X-ray. However, on March 17, 1932, a small lesion made its appearance in the right upper lobe. For some time it seemed to be nonprogressive, but on January 26, 1933, the patient reported, stating that she was three months pregnant. At this time, the X-ray shadow showed no change. However, on May 9, 1933, there was a definite extension of the lesion. She was advised to have artificial pneumothorax instituted on the right side. This was attempted on May 20, 1933, but unfortunately numerous adhesions were present over the right upper lobe preventing a good collapse. She gave birth to a normal infant on July 26, 1933.

Two children are included in this group (37 and 39). *Case 37* had a minimal reinfection type of disease in the right upper lobe. To our surprise, when artificial pneumothorax was instituted, the pleural space over the upper part of her chest was found to be completely obliterated. However, the treatments have been continued and, after six months of strict-bed rest, she returned to the Lymanhurst School, where she carries on the usual school activities. *Case 39* had a reinfection type of disease in both upper lobes. However, it was very slight on the right side. Partial artificial pneumothorax was instituted on the left side. The family refused any hospitalization or bed-rest, but were willing to have her admitted to the Lymanhurst School. She has done very well on treatment and has no symptoms. During the summer vacation of 1933, she failed to report when a refill was due. A considerable difficulty was experienced in convincing the family that the treatment should be continued. The family had taken her to a physician who had discouraged the continuation of

treatment on the ground that artificial pneumothorax is never indicated in a child because of the chest deformity that is likely to follow. The family was finally convinced by being told that artificial pneumothorax is a standard procedure among children, the same as among adults, when the reinfection type of disease is present. However, she discontinued treatments in June, 1934, and her general condition is excellent.

Thus, from this group of 52 cases, four have died (case 10 killed in accident, case 15 of miliary tuberculosis, case 21 of pneumonia and case 40 of multiple lesions), but we do not believe pneumothorax to have been in any way responsible. One has had extension of the lesion in the contralateral lung (9); in addition, this case had developed a fistula which resulted in empyema in the pneumothorax cavity. Three have had previously undetected lesions make their appearance in the opposite lung, which later required bilateral pneumothorax (18, 23 and 41); however case 23 has been restored to working capacity. Of the total group, forty-two are already working or ready to work. Since adhesions are responsible for many complications, such as empyema, which we have discussed elsewhere (54) (55), it is significant that among our 52 cases only three had adhesions sufficiently extensive to interfere with collapse. This confirms the contention that far better collapse and more satisfactory end-results are obtained if the treatment is instituted when the disease is in the minimal stage.

We are thoroughly cognizant of the fact that the time is too short since treatment was begun in many of this group of cases to determine the ultimate outcome. Tuberculosis is a relapsing disease and, years after lesions appear to be well under control, reactivations occur, but at present the results in this group are superior to those in other groups under our care, that had artificial pneumothorax instituted after the disease had become moderately or far advanced. They are also superior to those of other groups of minimal cases which we have observed on bed-rest treatment alone.

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THE DECOMPOSITION OF TUBERCULOPROTEIN, STARCH AND GELATIN BY DRY GRINDING[1]

C. H. BOISSEVAIN

The antigenic properties of tubercle bacilli are changed by dry grinding in a pebble-mill; they lose their acid-fastness and their power to provoke hypersensitiveness to tuberculin in guinea pigs after intraperitoneal injection (1). This may be due to the destruction of the structure of the bacterial cell or to some more profound change in the physical or chemical character of the cellular constituents. Alsberg (2) found that starch becomes soluble in cold water by grinding in a pebble-mill. Gelatin is rendered temporarily soluble in cold water and sets to a gel after some time. Alsberg considers this to be a physical change. The experiments described in the present paper show that, if the grinding is continued, the properties of the ground substance change so much that this can only be explained by assuming that the mechanical treatment has caused decomposition of the large molecules into smaller units. This decomposition apparently follows the same course as in acid hydrolysis.

EFFECT OF DRY GRINDING ON SOLUBLE STARCH

Five grams of soluble starch were ground in a Pyrex bottle making 30 revolutions per minute with 500 steel balls weighing 3,300 gm. The soluble starch dissolved in hot water, and gave a deep blue color with iodine. After 24 hours' grinding the starch had become soluble in cold water, as has been noted by Alsberg and Perry; the starch was somewhat contaminated by steel and glass dust, but could be conveniently separated from them by centrifugation; it still gave a blue color with iodine. After 168 hours' grinding, a solution of the ground starch gave a red color with iodine, and after 336 hours a drop of Lugol's solution did not produce any color, but, after adding several drops a faint pink appeared. At the same time the reducing power of 10 mgm. of the starch had increased from 0.001 mgm. dextrose to 0.31 mgm. dextrose. The starch had apparently been decomposed, first into erythrodextrin and then into

[1] From the Laboratory of the Colorado Foundation for Research in Tuberculosis at Colorado College, Colorado Springs, Colorado.

achroödextrin, with the simultaneous production of a small amount of dextrose, quite similarly to what we find in acid hydrolysis.

EFFECT OF DRY GRINDING ON GELATIN

Five grams of gelatin were ground in the manner described above. After 24 hours' grinding it was more or less soluble in cold water but formed a gel after some delay, as described by Alsberg and Griffing. After 96 hours' grinding, the gelatin had become completely soluble in cold water; a 10 per cent solution did not set to a gel, and its viscosity after a week in the ice-box was only slightly larger than that of water. A concentrated solution was not sticky but had the character of a syrup. This can best be explained by assuming that the gelatin had been changed into peptone, as happens in hydrolysis.

EFFECT OF DRY GRINDING ON TUBERCLE BACILLI

The tubercle bacilli were prepared for grinding by extracting them several times with ether, chloroform and water in succession, until only small amounts of lipoids and only the faintest trace of protein appeared in the washings. The lipoids were extracted to facilitate the extraction of all soluble protein. Five grams of tubercle bacilli that had been thus prepared were put in the ball-mill for 120 hours. At the end of this period no intact bacilli could be found under the microscope. Ether extracted 100 mgm. of lipoids from the ground bacilli and water extracted 1.7 gm. soluble material. This material may have preëxisted in the intact bacteria, but has been kept from diffusing by the existence of some membrane. The remaining 3.3 gm. was several times extracted with ether, with alcohol, and finally 10 times with water. This washing takes much time, as the ground and extracted bacilli form an opalescent suspension in water, which cannot be completely cleared even by several hours' centrifugating at 3,000 r.p.m. The washed residue was again put in the ball-mill and ground for another 48 hours. Extraction with ether at the end of this period furnished 26 mgm. lipoids (melting point 45°, phosphorus absent), and cold distilled water extracted 370 mgm. Trichloracetic acid in 10 per cent concentration precipitated 250 mgm. of protein from the watery extract; part of the remaining 120 mgm. could be precipitated by the addition of 20 volumes of absolute alcohol, but another part was soluble in 95 per cent alcohol and could be isolated only by evaporating the solution at room temperature, and removing the trichloracetic acid with ether. This material and the alcohol precipitate

were both very soluble in water, fairly soluble in 95 per cent alcohol and insoluble in absolute alcohol and in ether. Both fractions give strong biuret reactions; together they constitute the peptone fraction.

The insoluble residue was again washed several times until the washings showed no trace of cloudiness on the addition of 10 per cent trichloracetic acid. It was then dried and ground for another 48 hours. Extraction with ether gave now 21 mgm. lipoids, but water extracted 351 mgm., partly protein and partly peptone.

To compare the results of dry grinding with those of acid hydrolysis, 1 gm. of tubercle bacilli, freed from lipoids and soluble proteins in the manner described, was heated in a water-bath with normal hydrochloric acid for one-half hour. At the end of this period the material was centrifugated and extracted with water; 300 mgm. water-soluble protein was obtained in this manner, and 310 mgm. of material soluble in dilute alcohol and not precipitated by trichloracetic acid. Ether extracted 40 mgm. soluble material, and 125 mgm. residue remained. Water-soluble protein and a peptone with the same characteristics as those obtained by grinding can be obtained by acid hydrolysis, and the same changes in acid-fastness and in antigenicity appear after treatment with acids (1), as noted after grinding.

It seems justified to conclude that the changes brought about by dry grinding of the tubercle bacillus consist in the breaking up of the large antigenic molecule into smaller units. I have already mentioned a water-soluble protein and a peptone, but we can also isolate the specific polysaccharide from the wash-water after each grinding.

The residue obtained after three grindings and a hundred extractions had a composition resembling very closely that of the defatted bacilli. It contained 12 per cent nitrogen and 0.19 per cent phosphorus, and had a reducing power after boiling with hydrochloric acid corresponding to 3.3 per cent dextrose. This material is completely insoluble in water, ether or alcohol. If it is left over night in the ice-box in a 4 per cent sodium-hydroxide solution, it dissolves completely. This is however no simple solution but represents a chemical change. The insoluble compound cannot be recovered from the alkaline solution, but we can obtain an alkali-soluble protein, which forms the bulk of the material, a water-soluble protein, a peptone and the polysaccharide. If the insoluble residue is broken down by grinding instead of by treatment with alkali, no alkali-soluble protein but only water-soluble protein and peptone appear. Neither of them probably preëxist in the tubercle bacillus but

appear in different quantities according to the treatment to which the bacillus is subjected. No amount of grinding or washing could reduce the amount of phosphorus in the soluble residue to below 0.18 per cent, or the amount of specific polysaccharide below 3.33 per cent. A small amount of lipoids could usually be extracted after each grinding, but the amount becomes progressively less after each grinding, and we may assume that it is no integral part of the insoluble protein. The amount of phosphorus does not diminish after extraction with alcohol, ether, distilled water, slightly alkaline water or acidified water, and the amount of polysaccharide also remains constant under these manipulations. It seems probable that the insoluble residue consists of a compound of protein and polysaccharide and perhaps phosphorus.

Defatted bacilli are almost wholly built up out of this insoluble material. It can be destroyed by grinding, by treatment with cold alkali, or

TABLE 1

	NITROGEN	PHOSPHORUS	REDUCTION AFTER HYDROLYSIS CALCULATED AS DEXTROSE
	per cent	*per cent*	*per cent*
Tubercle bacilli	10.6	0.7	4.0
Defatted bacilli	11.4	0.17	3.3
Insoluble residue	12.0	0.19	3.3
Water-soluble protein	16.5	0.04	0.2
Alkali-soluble protein	12.0	0.14	0.32
Peptone	10.4	0.12	0.14

by boiling with dilute acid. The products of decomposition are alkali-soluble protein, water-soluble protein, peptone and specific polysaccharide. Their composition is compared with the composition of the tubercle bacillus in table 1.

Considering the ease with which the insoluble compound is broken up, it is not surprising that a certain amount of spontaneous hydrolysis takes place in cultures of tubercle bacilli, producing the well-known water-soluble protein, or tuberculin, and the specific soluble substance. From a six-weeks-old culture on synthetic medium I obtained 1.55 gm. bacilli and 0.025 gm. water-soluble protein, showing that less than 2 per cent had been decomposed during this period. The spontaneous decomposition of the substance of the tubercle bacillus does not stop at the water-soluble protein. We have seen that after grinding and after hydrolysis a peptone is obtained. The change from water-soluble protein to peptone also

occurs spontaneously. A solution of 20 mgm. of water-soluble tubercle protein (which had been prepared by precipitation with trichloracetic acid) in one litre of water was kept at room temperature for 6 weeks and then quickly evaporated at room temperature to a small volume, by means of a fan. Of the original 20 mgm. only 3 mgm. could now be precipitated by 10 per cent trichloracetic acid, while the remainder had changed into peptone with a corresponding loss of tuberculin activity.

SUMMARY

1. Prolonged grinding of starch causes it to change first into erythrodextrin and then into achroödextrin.

2. Prolonged grinding of gelatin changes it into a peptone-like compound, very soluble in cold water and unable to form a gel even at ice-box temperature.

3. Defatted tubercle bacilli consist mainly of an insoluble compound of specific polysaccharide and tuberculoprotein. This compound can be broken up by prolonged grinding into water-soluble protein, peptone and polysaccharide. Treatment with cold 4 per cent sodium-hydroxide solution or boiling with dilute acid has the same effect.

4. Water-soluble protein is hydrolyzed into peptone in very dilute solutions.

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A COMPARISON OF THE ANTIGENIC PROPERTIES OF DEFATTED TUBERCLE BACILLI AND THEIR DERIVED PROTEINS[1]

C. H. BOISSEVAIN

In the preceding paper (1) I have shown that the bulk of defatted tubercle bacilli is made up of an insoluble compound of tuberculoprotein and specific polysaccharide. This large molecule is easily destroyed by grinding or by treatment with boiling dilute acid or cold alkali. It is known that tubercle bacilli lose their power of producing hypersensitiveness on intraperitoneal injection as a result of prolonged grinding or of boiling with acids (2). The activity of the various decomposition products of the tubercle bacillus in producing hypersensitiveness in guinea pigs was tested to find the exact stage where this activity disappears. Most authors believe that only the intact bacilli can produce hypersensitiveness. Since Seibert claims that even the water-soluble protein can produce some degree of hypersensitiveness (3), varying quantities of all the antigens examined were injected into a series of guinea pigs to determine the minimum amount necessary to cause the appearance of hypersensitiveness to tuberculin. After three weeks the guinea pigs were tested with different dilutions of water-soluble tubercle protein to determine the degree of hypersensitiveness that had been established.

The following antigens were studied:

1: Defatted bacilli, prepared in the manner described in the preceding paper, by extraction with ether, chloroform and water.

2: Insoluble residue, the residue left after the third grinding and extraction described in the preceding paper.

3. Alkali-soluble protein, obtained by precipitating the solution in alkali of the preceding preparation with acetic acid.

4: Water-soluble protein No. 1, prepared by precipitating the filtered extract obtained after the third grinding described in the preceding paper, with trichloracetic acid, and washing the precipitate with alcohol and ether.

5: Water-soluble protein No. 2, similarly prepared from the washings of tubercle bacilli hydrolyzed with hydrochloric acid.

[1] From the Laboratory of the Colorado Foundation for Research in Tuberculosis at Colorado College, Colorado Springs, Colorado.

6: Water-soluble protein No. 3, similarly prepared from a filtered synthetic culture medium on which tubercle bacilli had grown.
7: Peptone, obtained from ground bacilli in the manner described in the preceding paper.

In the first place, the degree of tuberculin activity of each preparation was determined by injecting 0.1 cc. of different dilutions into guinea pigs infected four weeks previously with 0.01 mgm. H37 tubercle bacilli.

TABLE 1

Tuberculin activity of defatted tubercle bacilli and various of their decomposition products

TYPE OF TUBERCULIN USED	DILUTION					
	1%	0.1%	0.01%	0.001%	0.000,1%	0.000,01%
Defatted bacilli	4	4	4	4	2	0
Insoluble residue	4	4	4	4	2	0
Alkali-soluble protein	4	4	4	3	0	0
Water-soluble protein no. 1	4	4	4	4	2	0
Water-soluble protein no. 2	4	4	4	4	2	0
Water-soluble protein no. 3	4	4	4	4	2	0
Peptone	2	0	0	0	0	0

4 = Considerable infiltration and erythema with necrosis.
3 = Same but without necrosis.
2 = Slight erythema and infiltration.
1 = Erythema without infiltration.

Tuberculin activity disappears rapidly during the change from water-soluble protein to peptone, but is otherwise approximately equal in all the preparations tested.

Each of the preceding substances was now injected intraperitoneally into guinea pigs of approximately 400 gm., in quantities ranging from 1 to 100 mgm. At the end of three weeks they were all tested intracutaneously with increasing dilutions of water-soluble protein no. 3.

Reactions to tuberculin after injection of *defatted tubercle bacilli*:

QUANTITY OF ANTIGEN INJECTED	DILUTION OF TUBERCULOPROTEIN				
	1%	0.1%	0.01%	0.001%	0.000,1%
mgm.					
1 (two guinea pigs)	4.4	4.4	4.2	4.2	0.0
10 (two guinea pigs)	4.4	4.2	3.0	2.0	1.1
20 (two guinea pigs)	4.4	4.4	4.3	4.2	0.1
40 (two guinea pigs)	4.4	3.4	2.3	0.0	0.0

Reactions to tuberculin after intraperitoneal injection of *insoluble residue*:

QUANTITY OF ANTIGEN INJECTED	DILUTION OF TUBERCULOPROTEIN		
	1%	0.1%	0.01%
mgm.			
5 (two guinea pigs)	1.2	0.0	0 0
10 (two guinea pigs)	4.4	2.2	1.1
20 (two guinea pigs)	4.3	2.3	0.0
40 (two guinea pigs)	4.4	4.4	2.1
50 (one guinea pig)	4	3	0

Reactions to tuberculin after intraperitoneal injection of *alkali-soluble protein*:

QUANTITY OF ANTIGEN INJECTED	DILUTION OF TUBERCULOPROTEIN		
	1%	0.1%	0.01%
mgm.			
5 (two guinea pigs)	0.1	0.0	0.0
10 (two guinea pigs)	1.1	0.0	0.0
20 (two guinea pigs)	3.2	1.0	0.0
40 (two guinea pigs)	1.2	0.0	0.0

Reactions to tuberculin after intraperitoneal injection of *water-soluble protein no. 1*:

QUANTITY OF ANTIGEN INJECTED	DILUTION OF TUBERCULOPROTEIN		
	1%	0.1%	0.01%
mgm.			
10 (two guinea pigs)	1.3	1.1	0.0
20 (two guinea pigs)	0.0	0.0	0.0
40 (two guinea pigs)	0.3	0.2	0.0
100 (one guinea pig)	2	0	0

Reaction to tuberculin after intraperitoneal injection of *water-soluble protein no. 2*:

QUANTITY OF ANTIGEN INJECTED	DILUTION OF TUBERCULOPROTEIN		
	1%	0.1%	0.01%
mgm.			
10 (two guinea pigs)	2.0	2.0	0.0
20 (two guinea pigs)	1.0	0.0	0.0
40 (two guinea pigs)	1.2	1.0	0.0
80 (one guinea pig)	0	0	0

Reaction to tuberculin after intraperitoneal injection of *water-soluble protein no. 3*:

QUANTITY OF ANTIGEN INJECTED	DILUTION OF TUBERCULIN		
	1%	0.1%	0.01%
mgm.			
10 (two guinea pigs)	2.1	0.0	0.0
20 (one guinea pig)	3	0	0
40 (two guinea pigs)	3.1	2.0	0.0
100 (one guinea pig)	2	0	0

Reaction to tuberculin after injection of *peptone*:

AMOUNT INJECTED	DILUTION OF TUBERCULIN		
	1%	0.1%	0.01%
mgm.			
20 (two guinea pigs)	4.1	1.0	0.0
50 (two guinea pigs)	1.2	0.1	0.0
100 (two guinea pigs)	0.2	0.0	0.0

Under the conditions of these experiments, the hypersensitiveness caused by injections of defatted bacilli approaches that caused by tuberculosis. The insoluble residue obtained after grinding the defatted bacilli is still a good antigen, and causes hypersensitiveness, but a 1 per cent solution of tuberculoprotein is usually necessary to produce a four-plus reaction, while the same thing is done by a 0.01 per cent solution in the case of guinea pigs that have been prepared by injections of defatted bacilli. We can explain this by assuming that the insoluble residue is the first product of the breakdown of the antigenic complex in the tubercle bacillus. It is, however, still a complete antigen, has maximum tuberculin activity, causes the appearance of hypersensitiveness in the guinea pig, and it also causes the formation of typical tuberculous tissue with epithelioid cells and giant cells. This tissue reaction, although quite typical, is not as persistent as that found after injection of dead tubercle bacilli; after three weeks it has already started to retrogress and only rarely does it go on to caseation. The reaction to dead bacilli on the other hand persists several years and always becomes caseous.

Most of the antigenic activity is lost when the union between the protein and the polysaccharide is broken. The resulting water-soluble pro-

tein is still a most active tuberculin, but it does not cause the formation of tubercular tissue, and, if it ever produces real hypersensitiveness with type 4 reactions, its activity is very much less than that of the protein-polysaccharide complex. Seibert states that autoclaving should be avoided in preparing water-soluble protein, because of the "denaturing" effect of autoclaving. Undoubtedly autoclaving must cause some hydrolysis with resulting loss of tuberculin activity, and any intermediate stages on the way from insoluble residue to water-soluble protein would be hydrolyzed into water-soluble protein with corresponding loss of antigenic activity. I have tried to condense the water-soluble protein into a larger molecule by treating it with formalin during a long period. In this manner I obtained a small amount of insoluble material that was distinctly more antigenic than the original material and even caused the formation of some tuberculous tissue. But, as this condensation product always gave a positive Molisch reaction, it is possible that the formalin treatment only served to concentrate a small amount of nonhydrolyzed polysaccharide-protein compound present in the original material.

It is the compound of protein and polysaccharide which carries all the typical properties of the tubercle bacillus,—the production of tubercular tissue and of hypersensitiveness, and tuberculin activity. The soluble protein, which is one of the building stones of the antigenic complex, retains only the tuberculin activity.

The importance of the soluble protein, that is, of Old Tuberculin, among the products of the tubercle bacillus has been much overrated. A culture of tubercle bacilli produces 70 times more protein-polysaccharide complex than soluble protein; one milligram of defatted bacilli, free from soluble protein, makes a guinea pig sensitive to 0.001 mgm. tuberculoprotein, while 100 mgm. soluble protein is not quite sufficient to produce hypersensitiveness to a 1000 times larger dose. In other words, if the soluble protein plays any rôle in the production of the symptoms of tuberculosis, its importance is less than the one-millionth part of that of the polysaccharide-protein complex.

SUMMARY

1. Water-soluble protein obtained from ground bacilli, from hydrolyzed bacilli or from filtered culture media, all have the same tuberculin activity.

2. Doses of 1 to 40 mgm. defatted tubercle bacilli make guinea pigs

hypersensitive to 0.1 cc. of a 0.01 per cent solution of tuberculoprotein.

3. The same doses of the insoluble residue obtained by grinding make guinea pigs hypersensitive to 0.1 cc. of a 1 per cent solution.

4. It was not possible to make guinea pigs hypersensitive to a solution of 1 per cent tuberculoprotein by the injection of from 10 to 100 mgm. of any water-soluble or alkali-soluble protein or peptone derived from the tubercle bacillus.

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THE INTRACUTANEOUS (MANTOUX) TUBERCULIN REACTION

A Comparative Study of Positive and Negative Reactors

MEYER PARETZKY[1]

The recent years of modern technique in tuberculosis work have brought out many important facts hitherto unknown. The frequent use of the tuberculin test and of the X-rays, the follow-up system of contacts, and the search for the original cases responsible for the spread of infection, have resulted in a rapid accumulation of very important and highly interesting information.

Unfortunately, there is quite a divergence of opinion in the interpretation of the acquired material. The main issue of disagreement, very interesting in its theoretical part and still more important in its practical application, is the significance of the tuberculin reaction. All workers concur in that a positive tuberculin reaction means that tuberculous infection has been implanted into a living organism. But from there on disagreement takes place. According to one conception, it is not necessarily connected with an actual tuberculous disease and, furthermore, it bears some relationship to an establishment of a certain degree of immunity of the infected organism to subsequent doses of infection.

To quote the opinions of a few workers:

Rich and McCordock (1) state: "An animal infected with a sublethal dose of tubercle bacilli becomes, after some days, protected against subsequent infection with much larger doses of bacilli than the animal could have originally tolerated."

Wingfield (2) maintains that "childhood infection exerts a protective action as regards adult tuberculosis."

Heimbeck (3) says: ". . . . a positive reaction in a healthy person shows immunity against tuberculosis." He reiterates his statement in another work (4): "An infection that does not presently reveal its malignancy with symptoms of disease but merely causes allergy will seldom give rise to disease processes later; on the contrary, it protects the organism against new exogenous infection."

[1] Los Angeles, California.

Opie shares the quoted opinions to a certain extent only. In his belief (5), "The immunity conferred by the first infection is only relative and may always be overcome by massive infection." In a more recent work (6) he says: "With continued exposure to tubercle bacilli or even with repeated casual contacts with the micro-organisms such as evidently occur in children not exposed to household infection, sensitivity and presumably resistance is maintained."

Recently there has developed an entirely different interpretation of the significance of the tuberculin reaction. This new school does not draw a line of demarcation between infection and disease and considers every case of a positive tuberculin reaction as a potential case of an active disease.

Thus, Myers (7) says: "A positive tuberculin reaction . . . . is a definite liability." He also states (8): ". . . . every positive tuberculin reactor is a case of tuberculosis," and again (8): "We are no longer justified in speaking of tuberculous infection without disease, for they are one and the same thing."

Stewart (9) says: "So far as our evidence goes . . . . most, if not all, consumptive patients are derived by reinfection from the allergic group;" and he further states: "Apparently the opinion that infected individuals are protected, must be abandoned until indisputable proof to support this contention is found."

As we see, the interpretation of the early infection and of the positive tuberculin test divides the modern workers in the field of tuberculosis into different groups, some of which maintain diametrically opposed views. It is logical to expect that the same sharp division must arise with regard to the value of the absence of early infection as manifested by a negative tuberculin reaction. Thus, Heimbeck (4) maintains that "It is among those who, fortunately or unfortunately, have passed through childhood and the first years of youth without contracting a benign tuberculous infection that one finds an appalling morbidity from tuberculosis when they are exposed to infection."

And, *vice versa*, Myers (8) believes that "The uninfected human body is extremely resistant to tubercle bacilli." In another work (10), discussing the relative danger of exposure to infection for positive and negative reactors, he says: "If some have to be exposed, we firmly believe it should be the persons with negative tuberculin reactions."

Now, which conception is correct? What basic idea ought to be adapted as a foundation for practical procedures in the everyday tech-

nique of tuberculosis work? In all fairness to this vital issue we must admit that at present sufficient facts are not available to ascertain this issue in the direction of the remote prognosis. Our modern methods, so effective in bringing out information regarding our patients, are entirely too young. The solution must wait perhaps for another thirty to forty years till the children examined now in our clinics will travel far enough along the span of their lives. Perhaps even not ourselves but another generation of physicians will have an opportunity to reëxamine frequently enough a large number of these patients on whom we had started to work. And perhaps only this future medical generation will be able to obtain a definite reply to the question which is to be preferred, a positive or a negative tuberculin reaction.

However, we are in a position already now to study this problem in the direction of the immediate prognosis. Such attempts have been made by different workers, but again with different results.

A compilation of figures given by Heimbeck (4) on nurses,—probationers examined by him from 1924 to 1930 inclusive, shows that there were 11 cases of tuberculous disease among 401 positive reactors, or 2.7 per cent, and 69 cases among 226 negative reactors or 30.5 per cent. Geer (11) reports that out of 110 nurses admitted to the Ancker Hospital six had developed tuberculous disease, five of them gave negative tuberculin reactions on entering training.

On the other hand, Stewart (9) reports that out of 84 consumptive patients found in a group of 10,000 children examined at the Lymanhurst School only four were originally negative reactors and eighty positive. Myers (8) quotes the results of observations on 93,979 colored miners in South Africa during a period from April 1, 1928, to September 30, 1930; 65 per cent were positive reactors to tuberculin. Clinical tuberculosis had developed twice as often in the positive group as in the negative group. However, in the evaluation of these figures, one must introduce some corrections.

X-rays were not used during this investigation. It is clear to any experienced worker in the field of tuberculosis that a certain number of those whose reaction was positive would, if X-rayed, show radiographic evidence of disease already on first examination in spite of the absence of definite physical findings. In order to obtain a proper comparison between the positive and the negative reactors, this group, which had remained numerically unknown, ought to be subtracted from the number of active cases diagnosed during this survey.

Then again, the figures reported would be of value only if all reactors, the positive as well as the negative ones, would be placed in identical conditions with regard to exposure to tuberculous reinfection, which presumably could not be the case in such large numbers as the 93,979 miners observed.

We wish to report here the results of a study of contacts seen in some of the chest clinics of the Los Angeles County Health Department in the period between April 6, 1933, and February 15, 1934.

METHOD OF PROCEDURE

We realize that in order to be more conclusive this study ought to include all contacts examined. Unfortunately, a detailed analysis of a large group of several thousand patients was entirely impossible at that time.

We were compelled to limit our study to a survey of 37 families in which definite tuberculous changes had developed among those contacts that had a negative tuberculin reaction on earlier examinations. In these families we had studied all contacts regardless of the results of their tuberculin test. We hoped to obtain in this manner a comparison between positive and negative reactors, tuberculous and nontuberculous patients, belonging to the same families. We also have tried to study all observed varieties of tuberculous disease, pulmonary and nonpulmonary, arrested as well as active. We have also made an attempt to follow up the cases in which there were no other findings on first examination except a positive tuberculin reaction. Our aim was to find cases of active tuberculosis that would develop later among patients of this category. In spite of the fact that the past records were carefully surveyed each time a patient of this kind would come to our clinics, we had failed to find a single authentic case of active disease in this group. At the same time, using the same method of procedure, we had collected 43 cases of tuberculous changes that had developed among contacts previously negative to tuberculin, of which 23 were definitely active cases.

The intracutaneous test was used throughout. The customary dose was 0.1 mgm. for contacts of 1 year and older. For children of 6 months to 1 year, 0.01 mgm. was used, and 0.001 mgm. for infants younger than 6 months.

Special mention will be made whenever a deviation from these doses was made.

A total of 126 contacts was studied. There were 45 positive and 81 negative reactors, members of 37 families.

SEX, RACE, AGE RELATIONS

There was a slight preponderance of females over males in the negative group, and a more marked incidence of males over females in the positive group. Males had slightly exceeded females in the entire group studied.

The proportion of whites and Mexicans in almost all groups mentioned was approximately 1:2.7 respectively, which most probably had reflected the racial relationship of all our clinic patients correctly. As it will be seen later, different factors influencing the development of the cases were studied. The racial proportion had, however, undergone small variations during the different phases of the series.

The age of all contacts studied had shown a gradual and almost constant rise from infancy (4 for each of the first two years) up to the age of 8 years (17 for this group). There was a sharp slump for the age-group of 9 years (3 only); again a rise for the age group of 10 years (14) and later a gradual and almost constant decline down to 1 (age group of 25 years). The same tendency had manifested itself more or less for each of the two categories of reactors—the positive and the negative ones. The same general numerical relationship between positive and negative reactors (about 35 per cent and 65 per cent respectively) had repeated itself in the most of the separate age-groups. However, in 41 cases of previously negative reactors that became infected later the tendency was different: the figures were distributed quite evenly between all sex- and age-groups.

COMPARISON BETWEEN POSITIVE AND NEGATIVE REACTORS

In 22 of the studied families we were able to compare 45 positives and 42 negatives on first-application reactors. We felt that this comparison would be of some interest as both categories were placed under identical conditions. They lived in the same surroundings, ate the same food, used the same general hygienic and special prophylactic procedures, were exposed in the same degree to infection. The numbers of cases of these two categories are quite close (45 and 42) which makes the comparison so much easier.

The *diagnosis* for the positive reactors on first examination in two-thirds of the cases was not suggestive of any form of tuberculous process. The majority of the remaining one-third of the cases showed only the lightest forms of an arrested disease. Out of 16, five were cases of primary calcified lesions (Ghon tubercles), 4 of arrested tracheobronchial tuberculosis, and only 1 of arrested minimal pulmonary tuberculosis.

In 2 cases the question of activity was not decided (1 dry apical pleurisy, 1 accentuated hilar nodes); only 4 (less than 10 per cent) showed a definitely active tuberculous disease, but then again they were of the lighter types—1 tuberculous knee, 2 active tracheobronchial, and 1 active minimal pulmonary tuberculosis. We repeat again: the diagnosis of the patients of this group was quite favorable. (Table 1.)

The analysis of the findings on follow-up was quite instructive. (Table 2.) Ten cases (22.2 per cent) were not reëxamined. The remaining 35 were followed up for different lengths of time,—from one month to ten years, with an average of 1 year, 8 months, 16 days.

TABLE 1

Comparison of diagnosis on positive and negative reactors in 22 families

DIAGNOSIS	POSITIVE REACTORS		NEGATIVE REACTORS	
	Numbers	Per cent	Numbers	Per cent
Nontuberculous	29	64.2	18	42.8
Tuberculous knee, active	1	2.2	0	0
Primary calcified lesions	5	11.0	4	9.6
Accentuated hilar nodes	1	2.2	0	0
Tracheobronchial tuberculosis, arrested	4	8.8	2	4.8
Tracheobronchial tuberculosis, active	2	4.4	2	4.8
Dry apical pleurisy	1	2.2	0	0
Minimal, arrested	1	2.2	3	7.2
Minimal, active	1	2.2	6	14.4
Moderately advanced, active	0	0	4	9.6
Far advanced, active	0	0	2	4.8
A case receiving a small dose of O.T. applied at first had developed into a case of moderately advanced, active tuberculosis	0	0	1	2.4
Total pulmonary active cases	1	2.2	13	31.2
Total	45	99.4	42	100.4

The case of minimal active pulmonary tuberculosis became arrested. Out of 2 cases of active tracheobronchial tuberculosis, one remained unchanged and one became arrested.

The one with the tuberculous knee and also the one diagnosed as a case of accentuated hilar nodes remained unchanged on rechecks.

The case of dry apical pleurisy was not reëxamined. Nine out of ten arrested cases had remained unchanged on reëxamination; one was not reëxamined (a case of tracheobronchial tuberculosis).

Out of 29 cases which were free from any evidence of tuberculous in-

TABLE 2

Findings on further follow-up of positive and negative reactors in 22 families

DIAGNOSIS ON FIRST EXAMINATION*	TOTAL		REMAINED THE SAME		DEVELOPED INTO MODERATELY ADVANCED, ACTIVE		BECAME ARRESTED		NOT RE-EXAMINED		REMAINED THE SAME		IMPROVED		DIED		PLACED IN SANATORIUM		NOT RE-EXAMINED		TOTAL	
	Numbers	Per cent	Numbers	Per cent	Numbers	Per cent	Numbers	Per cent	Numbers	Per cent	Numbers	Per cent	Numbers	Per cent	Numbers	Per cent	Numbers	Per cent	Numbers	Per cent	Numbers	Per cent
Nontuberculous	29	64.2	20	44.4	1	2.2			8	17.8	18	42.8									18	42.8
Tuberculous knee, active	1	2.2	1	2.2																		
Primary calcified lesion	5	11.0	4	8.8					1	2.2									4	9.6	4	9.6
Accentuated hilar nodes	1	2.2	1	2.2																		
Tracheobronchial tuberculosis, arrested	4	8.8	4	8.8							2	4.8									2	4.8
Tracheobronchial tuberculosis, active	2	4.4	1	2.2			1	2.2					2	4.8							2	4.8
Dry apical pleurisy	1	2.2							1	2.2												
Minimal, arrested	1	2.2	1	2.2							1	2.4							2	4.8	3	7.2
Minimal, active	1	2.2					1	2.2					3	7.2			2	4.8	1	2.4	6	14.4
Moderately advanced, active																	4	9.6			4	9.6
Far advanced, active															1	2.4	1	2.4			2	4.8
Those in which small dose of O.T. applied at first developed into moderately advanced, active																	1	2.4			1	2.4
Total	45	99.4	32	70.8	1	2.2	2	4.4	10	22.2	21	50.0	5	12.0	1	2.4	8	19.2	7	16.8	42	100.4
	Contacts positive to tuberculin										Contacts negative to tuberculin											

* Initial diagnosis in both groups as made on first examination after the first positive tuberculin test.

volvement on first examination 8 were not reëxamined, 20 had remained unchanged, and one was diagnosed later as moderately advanced pulmonary tuberculosis, placed in a sanatorium, and died there. However, the history of this case contains a chain of events of such unusual sequence that we deemed it necessary to describe this case separately.

Family D had lost two boys of tuberculosis, one in 1927 and one in 1929. Mother was diagnosed in 1933 as minimal active. In spite of a thorough search, during which all relatives and most of the close neighbors were examined, no other cases of tuberculosis were found among adults. Antonia, female, born in 1919, had her first tuberculin test on December 17, 1930, which was positive. Unfortunately, an X-ray appointment was not kept. On reëxamination, February 17, 1932, the intracutaneous test was negative. We are convinced that both tuberculin-test readings were correct. The patient was brought to the clinic, May 10, 1933, with a history of a recently developed "cold" with cough and expectoration, was diagnosed as a case of moderately advanced pulmonary tuberculosis, with cavity-formation in the right upper, and with sputum positive. X-ray confirmed the physical findings. The girl was placed in a hospital and later in a sanatorium; her case progressed there to a far-advanced stage. She died in December, 1933. It is interesting to note that her brother Manuel, born in 1916, who had a negative intracutaneous test twice in 1931 and 1932, had broken down at the same time and was diagnosed as a case of far-advanced tuberculosis, while two younger sisters, who had positive intracutaneous tests and negative X-rays in 1930 and 1932, had remained well in 1933. In other words, this girl Antonia, was well while she had a positive tuberculin reaction, but broke down with tuberculosis when her reaction had changed to negative. This agrees with what Opie had said (5): ". . . . immunity diminishes when recovery appears and disappears after the (first) lesion has completely healed. Only the tuberculous animal is immune."

The case cited illustrates clearly the protective value of the positive tuberculin reaction.

There were 42 cases in the same 22 families that had a negative intracutaneous reaction on first application. They were all diagnosed then as nontuberculous. On further examinations (table 1) 18, or 42.8 per cent, had remained nontuberculous, in comparison with 29, or 64.2 per cent, of the previously described group. Nine cases were diagnosed as arrested: primary calcified lesions 4, the same number as in the positive group; arrested tracheobronchial tuberculosis 2, the same as in the positive group; minimal arrested tuberculosis 3, against 1 in the positive group.

There were 15 active cases in this group, against 3 in the positive group. Tracheobronchial tuberculosis 2, same as in the positive group; minimal pulmonary tuberculosis 6, against 1 in the previous group; moderately advanced tuberculosis 5; and far-advanced tuberculosis 2 cases. However, we must mention that one of the moderately advanced cases had on first application a smaller than usual dose of tuberculin. We wish to emphasize that there were no cases of advanced pulmonary tuberculosis among the positive tuberculin reactors.

It is obvious that the negative group had developed a great deal more tuberculosis than the positive group. The active forms were predominating, with a great proportion of markedly advanced forms of pathological processes.

The further progress of the negative group was quite interesting (table 2). On further follow up all 18 nontuberculous cases had remained unchanged. The 4 cases with primary calcified lesions were not reexamined. The 2 arrested tracheobronchial tuberculosis cases had remained unchanged. The 2 cases of active tracheobronchial tuberculosis had improved, but none became arrested, while of the same number in the positive group one became arrested. Out of 3 cases of minimal arrested tuberculosis, 2 were not reëxamined, and 1 had remained the same. Among the 6 cases of minimal pulmonary active tuberculosis, 1 was not reëxamined, 3 had improved, and 2 became worse and were placed in sanatoria. All 5 cases of moderately advanced pulmonary tuberculosis had to be placed in sanatoria; of the far-advanced cases 1 was placed in a sanatorium and 1 died. Altogether in this small group there were 1 death and 8 sanatorium placements. The above comparison between the positive and negative reactors had demonstrated the great difference in their diagnosis and prognosis. How much worse was the fate of the negative group.

Why then did the tuberculous infection bring such different development to members of the same families otherwise subject to the same conditions?

We wish to suggest the following explanation. The positive reactors were infected earlier when the cases spreading infection were not yet badly stricken by the disease. Those contacts who at that time had a negative tuberculin reaction had escaped infection. Later the condition of the infecting patients became worse. Their infection and consequently its dosage transmitted to the contacts had increased. The positive reactors were by this time protected by the previous smaller doses of infection against the subsequent larger ones. The negative reactors had

remained unprotected since the previous exposure, could not therefore successfully resist the later massive doses, and had consequently developed different forms of the disease.

ANALYSIS OF THE ENTIRE NEGATIVE GROUP

As we had said before, there were, in 37 families studied, 81 contacts who had a negative intracutaneous reaction on first application. Of them 38 had remained nontuberculous, and 43 had developed various forms of tuberculosis. Among those 43, we had 2 cases in which the initial tuberculin dose was very small. They developed later tuberculous changes: one was diagnosed as moderately advanced pulmonary tuberculosis and was placed in a sanatorium, another developed calcified primary lesions.

The remaining 41 were distributed as follows: Primary calcified lesions, 4; tracheobronchial tuberculosis arrested, 5; tracheobronchial tuberculosis active, 2; dry pleurisy, 1; minimal pulmonary tuberculosis arrested, 9; minimal pulmonary tuberculosis active, 10; minimal pulmonary tuberculosis, active with pleurisy, 1; moderately advanced pulmonary tuberculosis, active, 6; far-advanced tuberculosis, active, 2; and tuberculous meningitis, 1.

Some of the arrested cases were not reëxamined; the balance had remained unchanged.

Of the 10 cases of minimal pulmonary tuberculosis, active, 2 were not reëxamined, 4 had improved, 1 became worse, 2 were placed in sanatoria, and 1 died. However, the exact immediate cause of death in this last case had remained unknown, and the diagnosis was between tuberculous meningitis and acute mastoiditis.

All 6 moderately advanced cases became worse and all but one were placed in sanatoria.

Of the far advanced cases 1 died and 1 was placed in a sanatorium. The case of tuberculous meningitis died. Both cases, in which pleurisy was diagnosed, were not reëxamined.

Altogether, there were in the group of primarily negative reactors 3 deaths and 9 sanatorium placements.

On follow-up rechecks of 38 negative reactors that had remained nontuberculous the intracutaneous test was not repeated in 6, in 13 it had changed to positive and in 19 it had remained negative on later applications. It is noteworthy that, in this last category, in 2 cases the patients responsible for the spread of the infection died before the contacts were

examined; in 13 cases the contact was interrupted early; in 1 case the contact was very irregular and in 3 cases the source of the infection had remained unknown; in other words, the exposure was only accidental.

We see that in all cases in which the primarily negative reactors had remained nontuberculous there was either a short exposure to infection or a change from a negative to a positive tuberculin reaction, which apparently had served as a protective measure against subsequent massive doses of infection.

On the whole, the prognosis of our negative reactors was considerably worse than in the series of exposed nurses studied by Heimbeck (4) and Geer (11). We explain this observation by the fact that our cases were more intimately exposed to infection in their homes than nurses could possibly be in hospitals.

RÔLE OF MASSIVE INFECTION

We have tried to study the conditions under which our negative reactors became infected. We had noticed that two-thirds of the infected contacts were exposed to massive infection,—to patients who were diagnosed as moderately and far-advanced cases, and in 8 instances to more than one open case of tuberculosis at the same time. In this category we have most of our worst infected cases. Here belong all our cases of tuberculous meningitis, of moderately advanced pulmonary tuberculosis, of active tracheobronchial tuberculosis; about 50 per cent of far-advanced pulmonary tuberculosis, of minimal active and arrested cases; and all but one of each primary calcified lesions and arrested tracheobronchial tuberculosis. In almost all instances in which the disease in the contacts exposed to massive infection had manifested itself in lighter forms or became arrested, we had established that the exposure was interrupted early. Observations mentioned here correspond to the opinion expressed by Krause in regard to the significance of massive doses of infection in relation to advanced types of tuberculous disease (12).

It is interesting to note that exactly 50 per cent of our cases of minimal pulmonary tuberculosis, active, were infected by patients who were diagnosed as arrested: minimal 4, and moderately advanced 1. In two instances we had definite proofs that the change of the intracutaneous reaction in the contacts from negative to positive had taken place at the time when the supposedly arrested members of the family had suffered a flare-up of activity.

In 2 cases of minimal arrested tuberculosis we could not find any other possible sources of infection besides a draining tuberculous knee in one case and objects belonging to a member of the family, who died of tuberculosis, in another case.

In 17 cases we had a record of positive sputum, expectorated by patients responsible for the spread of the infection. However, we could not establish a predominance of more advanced types of the disease in the respective contacts. Perhaps it was due to the reason that many of the spreaders of the infection were not long enough under the care of the clinics to give us as high a number of positive-sputum specimens as could be expected.

Ten of the spreaders of the infection were placed in sanatoria. It is interesting that 6 of the contacts in this category were arrested cases (2 tracheobronchial, 4 minimal pulmonary). Two were cases of active tracheobronchial tuberculosis, 1 of minimal active tuberculosis with dry pleurisy, and only 1 of moderately advanced pulmonary tuberculosis. In other words, the interruption of the contact had resulted in a better prognosis for this category.

And there was a striking difference between this last category and another consisting of 9 cases in which the carriers of the infection died. The contacts here were diagnosed: tuberculous meningitis 1, moderately advanced 3, minimal pulmonary tuberculosis active 2; and calcified primary lesions, tracheobronchial tuberculosis arrested, minimal pulmonary tuberculosis arrested, one of each. Here is clear evidence of the danger of exposure to massive infection, as in this instance it had produced rather more active types of the disease. In 4 cases the source of the infection had remained unknown; only in one case the infection had originated from close neighbors. In the rest of the cases (38) the infection was contracted in the same house from immediate members of the family.

We had only quite an inexact way of determining the length of the exposure, from the date of the first negative intracutaneous reaction to the date of the definitely made diagnosis of pathological process in the contact or to the date of interruption of exposure. The length of the exposure had varied in our series from 1 month to 2 years, 1 month and 22 days.

In some of the cases we were able to demonstrate the influence of the prolonged exposure which would result in producing a more advanced

type of the disease in the contacts. However, in other cases one could get an impression that a shorter exposure would be also instrumental in producing advanced forms of tuberculosis. But, we must take into consideration that in many of these instances the actual exposure was certainly much longer than it appeared, because of the fact that the spreaders of the infection were not always available for examination in the earlier stages of their disease.

THE CHANGES OF THE INTRACUTANEOUS REACTION

Our attempt to follow the changes of the intracutaneous reaction in the *positive group* were not entirely successful, because in about 50 per cent of the cases the reactions when read were not classified into different degrees, but were reported by a general term "positive." Besides, in about one-third of the cases studied the test was not repeated. However, in all cases in which the test was repeated, we had noticed that it had a tendency either to remain of the same degree or to decrease. Only in one case did we see an increase,—a change from 1 plus to 3 plus.

The positive group did not show any connection between the degrees of the reaction and of the pathological changes. The majority of cases of different degrees of the reaction did not reveal any evidence of tuberculous involvement. It is interesting to note that the only case of active pulmonary tuberculosis diagnosed in this entire group had a 1-plus reaction. In the negative group the reaction on follow-up gave the following data:

In the 2 cases in which too small a dose of tuberculin was applied at the beginning, the change was to positive in one case and 2 plus in another. Of 41 reactors negative to 0.1 mgm. that later developed signs of tuberculosis, the test was not repeated in 10 cases. In the others it was read as 1+ in 6, 2+ in 6, 3+ in 4, 4+ in 1, and "positive" in 14. The data on the 38 negative reactors that remained nontuberculous were as follows: test not repeated in 6, remained negative in 19, and changed to positive in 13. Of these 13 it was read as 1+ in 3, 2+ in 4, 3+ in 1, 4+ in 1, and "positive" in 4.

EARLY CALCIFICATION

We wish to report that we had seen 5 cases in which calcification was radiographically demonstrated very shortly after the introduction of the infection,—within from 3 months and 15 days, to 4 months and 25 days

after the date of the last negative intracutaneous test. Of these two were cases of calcified tracheobronchial, 2 of minimal arrested, and 1 of minimal active tuberculosis. In view of the early age of the contacts and of definitely established source of the infection in each case, we felt that this calcification could not possibly exist before the reaction had changed from negative to positive.

SUMMARY AND CONCLUSIONS

1. A very brief review of the current literature demonstrated a great difference of opinion in regard to the relationship between early mild tuberculous infection and immunity to tuberculosis.

2. A comparison of numerically almost equal groups of positive and negative tuberculin reactors that belonged to the same families showed that both diagnosis and prognosis were considerably more unfavorable for the negative group.

3. The "dosage" of the infection and the length of exposure were found to be factors of great importance which had influenced the developments among the negative reactors who later showed evidences of tuberculous disease.

4. The negative reactors that remained nontuberculous were either removed from the source of the infection or had acquired a positive tuberculin reaction.

5. In accordance with the above observations we practise in our work, as a prophylactic measure, early interruption of exposure, as much as possible, in all cases (with all kind of contacts, positive and negative) and especially in cases of massive infection. Special attention is paid to negative reactors if for some reason they remain exposed to infection; they are frequently reëxamined and are otherwise closely watched.

In conclusion we wish to express our appreciation to Dr. P. K. Telford, Chief of the Tuberculosis Division of the Los Angeles County Health Department, for his permission to use the clinic cases for this report; to Dr. C. Walser, chest clinician, who kindly allowed us to use 3 cases observed by him; and to Dr. M. L. Pindell, roentgenologist, who assisted in the interpretation of the X-ray films.

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LOCAL SKIN REACTIONS IN MEASLES AND SCARLET FEVER IN RELATION TO THE INTRACUTANEOUS TUBERCULIN REACTION[1]

J. D. PILCHER

It is known that the cutaneous tuberculin reaction is lessened during certain acute diseases, notably measles and influenza, and during tuberculosis, especially in its later stages, as the patient loses weight and becomes emaciated. The latter condition has been discussed in earlier papers (1), where it was suggested that decrease in tuberculin sensitivity under such conditions was due, in part at least, to lessened local circulation secondary to tissue loss and dehydration, inasmuch as other nonspecific skin reactions followed the same course.

Three tuberculosis subjects under study at that time contracted measles; during their illness the skin sensitivity to tuberculin decreased markedly, as did also a nonspecific skin reaction; and because of this it was thought that the decrease in the tuberculin sensitivity during measles infection was probably due not to loss of "allergy" in the strict interpretation of the condition, but to a lessened circulation in the skin and subcutaneous tissue. It is known, too, that other reactions lessen or fail during measles and other infectious diseases, such as vaccination against smallpox, reactions to foreign protein, and the Wassermann and Widal reactions (Netter and Porak (2)).

Recently there has been an opportunity to complete the study of the question of local nonspecific reactions in the contagious wards of the Cleveland City Hospital during two epidemics: a first study was made during the hot summer of 1931, and the second in the winter of 1931–1932. The results were similar in the two series, and are discussed together. Repeated observations were made on 38 white and 17 negro children, and single observations on others, the subjects varying in age from 4 months to 11 years. In the majority of subjects five to six observations were made; in some instances more (up to 12), and in the later cases fewer. A total of well over 200 observations on measles

[1] From the Departments of Pediatrics and Contagious Diseases of the School of Medicine, Western Reserve University, and of City Hospital, Cleveland, Ohio.

patients was made. It was thought to be improbable that a sufficient number of tuberculin-positive measles cases could be had in a reasonable time to draw definite conclusions as to the course of the tuberculin reaction in measles; hence the main motive of the investigation was to learn the effect of measles on a nonspecific skin reaction, depending on the reports of others, first by Pirquet (3) and by Eddy and Mitchell (4), that the tuberculin reaction is definitely lessened during measles and other diseases. However, tuberculin tests were made on the greater number of the patients, only a few of which gave positive reactions.

METHOD

As in previous studies, the wheal following the intracutaneous injection of a codeine solution was used as an example of a nonspecific reaction. Since the reaction was to be determined from day to day during the course of the measles infection in infants and children, it seemed more feasible and as accurate to follow Lewis's (5) puncture method rather than the intracutaneous injection. A small drop of a 1 per cent codeine sulphate solution was placed on the skin of the forearm toward the elbow and a second drop toward the wrist. A single puncture into the skin through the upper drop was made by a hypodermic needle with the needle held horizontally, and through the skin through the lower drop with the needle held vertically. As with the injection method, in a normal subject a wheal arises at the puncture point surrounded by a reddened area which reaches its maximum in about 10 minutes, and gradually disappears during the course of 30 to 40 minutes. The wheal area is readily palpated. The puncture reaction nearer the wrist was smaller, as a rule, than the upper one, but otherwise there was no difference in the two reactions. In an average, well-nourished child the wheal is usually round or oval in shape and will reach measurements of from 4 to 6 mm. in diameter, occasionally becoming larger. However, the degree of a reaction is measured by the amount and persistence of the induration rather than by the dimensions of the wheal, and for this reason it is difficult to express the degree of the reaction in figures; but, in the cases cited, the diameters of the wheals corresponded to the amount of induration, thus saving the introduction of other terms. As the reddened area or erythema about the wheal is usually roughly proportional to the wheal's size, it has been disregarded in this report.

Individuals may vary somewhat in their local reaction to irritants (codeine as an example). Although there are occasional exceptions, well-

nourished persons and those with fine, delicate skin react better than the undernourished and those with harsh, rough skin; and chronically dehydrated better than acutely dehydrated persons.

Experience in the method enables one to judge fairly well from the appearance of the subject the nature of the expected reaction, but here again one's judgment occasionally is wrong. During a measles infection one estimates the degree of the local reaction as compared with that in normal children and with the result during convalescence in the same patient to determine the individual's variation in reaction. Inasmuch as many children lose weight during a measles infection and may not regain it during the stay in the hospital, it is questionable whether the normal reaction, that is, the one for the subject in normal health, was seen in such cases. It happened, however, that the reaction was uniformly larger at or near the time of discharge from the hospital than during the height of the disease; hence the former served as the normal for the individual. Several children were seen some time after convalescence, and in each instance the local reaction was considerably larger than when the patient was discharged from the hospital. Figure 2 illustrates the average wheal.

Because it is known that oedema of the skin, including urticaria, lessens and may even abolish the codeine wheal-formation, the injections were made into clear or non-rash areas whenever possible, comparing the reaction in such places to an injection made at the border of or directly into a confluent eruption.

PROCEDURE

In the great majority of subjects the examinations were made shortly after admission to the hospital, when the rash had already appeared. Several patients in the pre-rash stage, as diagnosed by the presence of Koplik's spots, were sent to the hospital from the Out-Patient Clinic. Thus there was an opportunity for observation before the onset of the rash. A number of measles contacts were also examined. Only two of these developed measles; hence, but two subjects were examined before the onset of the disease, and during and after it. In a previous publication it was noted that 3 patients who were studied in this manner during the course of measles lost considerable weight, and that the local (codeine) and tuberculin reactions decreased during the period of loss and increased as the weight returned to normal. It was not possible to weigh the subjects examined in this series and thus to compare the relation of skin reactions to the weight curves, but without question many of the patients did lose weight during the acute stage of the disease.

RESULTS

In brief, during the measles infection, practically without exception, the cutaneous reactions from the codeine injections were small during the rash stage and became larger (increasing toward the normal if not actually to it) in the period of convalescence. In general, the more severe the disease, the greater the decrease in the cutaneous reactions; at times the wheal-formation was almost negligible. Occasionally, however, a very sick patient gave a considerably larger reaction than was expected, one that approached some of those seen in normal subjects; although in all such instances the later reactions in convalescence were distinctly larger. Sometimes, when the infection was rather mild, the reactions were smaller than was expected; usually the reason for this was not clear. It should be emphasized that the reactions at different stages of the infection are comparable, actually, in the same patient only; in other words each subject has his own standard or size of wheal-formation.

Citation of the following cases will illustrate most of the points in question:

An average, well-nourished negro boy, aged 3 years, had been exposed to measles 7 days before the first skin test was made. The temperature was normal. At this time the wheals measured 5.5 x 6 mm. and 5 x 5 mm. in diameter and were well raised above the surrounding skin and well indurated; the reaction was the greatest of those in several children examined at the same time. Three days later the temperature rose to 39.5°C., and there were a very few minute papules on the arms and body, suggestive of measles; the wheals at this time measured 2.5 and 1.5 x 1.5 mm., and were flat and scarcely palpable. The next day the rash was general; temperature 40°C.; the patient was rather ill but not prostrated; and dehydration was not observed. Three wheals measured about 2 x 2.5 mm., and were again flat but little indurated, and faded promptly. Two days later the temperature had fallen to 38.5°C.; the wheals were larger, 4 x 5 and 4 x 4 mm., but still measured less than the patient's normal reaction. There was evident loss of weight and convalescence was rather protracted; the local reaction remained small, returning to normal about two weeks after the appearance of the rash; the wheals on the 16th day of the disease measured 5 x 5 mm. and 4.5 x 6 mm. and were raised and indurated as they were before onset of the disease.

Time of Appearance of Decrease in Reaction

It has been stated that during the measles infection the local skin reaction becomes lessened, to return to normal during convalescence. From the nature of the local reaction (wheal) it was not possible to determine

exactly the time at which the maximum decrease took place; however, of the patients seen previously to or on the day of the appearance of the rash, 20 showed the maximum decrease on the first day of the rash, 10 on the second day, and an occasional one on the third or fourth day. It is noteworthy that of the 9 patients seen in the pre-rash period none gave the maximum decrease in the wheal-formation during this stage, although two-thirds of them did show a somewhat lessened reaction on the day preceding the rash. Some of these patients were rather ill, too, during this period. As the temperature fell to normal and the rash faded the patients' general condition improved. In the majority of cases the local reactions also returned to, or approximately to, the normal, usually on from the fourth to the sixth day. When convalescence was delayed, however, especially if there had been considerable loss of weight, there was also delay in the return of the wheal formation to the normal. No doubt many of the patients did not at any time show what we may choose to call their normal reaction, for they were probably below their normal physical condition while in the hospital, as was evidenced by the fact that a much larger reaction than was found previously was given by some who were reëxamined several weeks after discharge from hospital.

Results in the Negroes

There were 17 negro children in the series, aged from 4 to 8 years. All but one of them had fairly severe infections which differed in character from those of the white children only in the nature of the rash, which consisted of discrete or small groups of fine papules. In no case was the rash on the arms macular or confluent (blotchy); this permitted tests to be made both in clear and in rash-involved skin. These patients were examined at all stages of the disease, pre-rash, rash and convalescent. The results were similar to those obtained in the white children and were grouped with them in the summaries.

Relation of Fever to the Local Reaction

Fever seemed to bear no definite relation to the local reactions. Among the patients first examined early in the course of the measles infection, the maximum decrease in wheal-formation was fairly evenly divided between the periods of high fever and those when the fever returned to normal, or there was the same decrease in each of these periods. In a former publication (6) it has also been noted that fever had no apparent effect on wheal-formation from the intracutaneous injection of codeine solution. There are not sufficient data in the pre-rash series to warrant deductions in this respect.

Scarlet Fever

In a smilar manner the local reaction was investigated in scarlet fever in children and in adults. The results were fairly proportional to the severity of the rash; when the rash was marked the reaction was almost negligible, and when it was slight or fading the reaction was larger and approached the normal for the individual. The normal was considered to be the reaction several days or more after the disappearance of rash and fever. No opportunity was given to examine patients before the onset of scarlatina.

To give an example:

A well-nourished 3-year-old girl had a well-marked scarlet rash on arms, body and thighs, and a fading rash on the face; temperature, 38.6°C. At one puncture site, no wheal developed; at the second site there was a minimum reaction. Ten days later, when the rash had gone, average wheals were formed.

Other patients with well-marked rash gave positive reactions, and at times slight induration could be palpated although no wheal was visible and a flare could be seen as a deeper flush about the puncture site. There was but a single opportunity to examine a skin of the forearm showing different degrees of erythema, and in this instance the reaction in the redder area was less than that in the paler area, as was expected. The absence of whealing in the rash area and the whealing during convalescence are shown in figures 1 and 2.

As the flush from atropine resembles that of scarlet fever, a few codeine skin-tests were made on subjects with atropine flushes. These subjects were limited in number, as the flush from atropine commonly involves the face chiefly and to a limited degree the trunk and extremities, and it did not seem feasible to make the tests on the skin of the face. As in scarlet fever, the reaction to codeine was roughly proportional (inversely) to the degree of the rash, very slight (practically absent in one subject) when the rash was marked, and merely lessened in the milder flushes. These tests were controlled in the same areas the following day when the flush and other atropine effects had disappeared, and in each subject the codeine reaction was much larger than during the atropine flush.

DISCUSSION

It has been noted that the codeine reaction was lessened not only directly at the site of the rash of measles, that is, in or immediately adjacent to the macules, but (a fact which is of much greater interest) in

areas free from rash and in patients who also had a very mild infection with very few macules on the arm. Lewis (7) suggests that the rash of measles depends upon the liberation of a histamine substance (his H-substance), and has noted that "the rash of measles shows refractoriness to histamine itself;" a similar explanation would seem to apply to the results here with codeine. A second factor is that of oedema of the skin, for clinically the puffiness of the skin, of the face especially, is usually present when the rash is at all marked, and Mallory and Medlar (8) in their histological studies of the excised skin of measles patients noted exudations of serum and endothelial leucocytes, a process which led to swelling and vacuolation of the epithelial cells and to formation of minute vesicles beneath the cornified layer. It is, of course,

Fig. 1

Fig. 2

Figs. 1 & 2. Codeine punctures into the skin of the forearm at the height of scarlatina rash and after the rash had faded. Fig. 1 was taken at the height of the rash and shows no wheals formed. Fig. 2 was taken one week later when the rash had disappeared; two well-formed wheals are visible.

well known that oedema, even when very slight, lessens and, in more marked degrees, may abolish wheal-formation. Whether the lessening of the wheal-formation in uninvolved areas of skin is dependent upon similar factors is not disclosed by the evidence at hand.

Regardless of the rash itself, there is probably no doubt that in severe measles infections, with great prostration, local reactions will be lessened, as has been reported previously (1). Debré and Papp (9) and Lereboullet and Baize (10) have stated that the local reaction to tuberculin is lessened in proportion to the severity of the disease, although they do not distinguish between the degree of prostration and the intensity of the exanthem.

Lewis (6) has demonstrated that the skin of the forearm when heated by immersion in water to certain temperatures does not wheal. This he attributes to the fact that the whealing substance (H-substance or actual

histamine) is washed away more quickly when the blood flow to the skin is rapid. Histological examination of the skin of scarlet-fever patients has shown vascular dilatation, as would be expected. Whether there is actual oedema of the skin seems to be disputed by pathologists (Kritch (11)); but certainly, clinically, parts of the body show oedema when the rash is marked. The skin flush from atropine is also due to vascular dilatation. It is probable, then, that lessened codeine whealing in scarlet fever and in atropine flush is due to prompt washing away of the codeine solution, with the factor of oedema playing a minor rôle in the case of scarlet fever.

CONCLUSIONS

The activity of the nonspecific whealing agent (codeine solution) is lessened, and may be practically abolished, in measles, scarlet fever and atropine flush, as is also the local reaction to vaccine virus, to foreign products and to other agents as reported in the literature. In view of this finding it is considered that the factors that produce this result, namely, refractoriness, oedema and washing away of the irritant by the effect of rapid circulation (as in scarlatina and atropine flush), also influence the reaction to tuberculin in these conditions.

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TUBERCULOSIS AMONG UNIVERSITY WOMEN

RUBY L. CUNNINGHAM[1]

This study is based upon an experience (as Physician for Women) with tuberculosis among women at the University of California from 1920 to 1933, a period of fourteen years. All students are given a physical examination when they matriculate. Those seeking entrance to the professional schools (librarianship, nursing, social service, education and medicine) are reëxamined. Opportunities for contact between the student and the physician are offered by the dispensary and hospital and, since these services are without added cost to the student, they are freely used and often bring to attention minor deviations from normal health as well as symptoms of more serious nature.

Approximately 20,000 women have been in attendance at the University during the fourteen-year period of this study. College days usually fall between the fifteenth and twenty-fifth years of life, and by far the largest number of the 20,000 were in this age-group. However, during recent years, insecurity of occupation and interest in adult education have brought many older women to the University.

The diagnosis of active pulmonary tuberculosis was made for 187 of the 20,000 students. (Chart 1.) The youngest was seventeen years old and the oldest fifty-four years. Twenty-nine, the largest number for any age, were nineteen years old. Forty-six were more than twenty-five years of age.

The number of cases discovered per year varied from five to twenty-one. (Chart 2.) During the first three years of this study, five, eight and seven cases respectively, were discovered; during the second three years, twenty-one, fourteen and eighteen. No cause is apparent for the sudden increase in the number of active cases of tuberculosis found. The method of examination, membership of the staff, and interest in the subject did not change at that time. Since 1932 there has been a more determined effort made to find more tuberculosis and to find it earlier. The intracutaneous tuberculin test has been much more frequently used than formerly, and all students giving histories suggestive of tuberculosis

[1]The Ernest V. Cowell Memorial Hospital, Berkeley, California.

or of family contact have been carefully studied. It was expected that this would increase the number of cases discovered, but, instead of more, fewer cases of tuberculosis have come to light in 1932 and 1933 than in the years immediately preceding.

In many instances, attempts were made to discover the source of infection. These were seldom successful. In only one instance did it

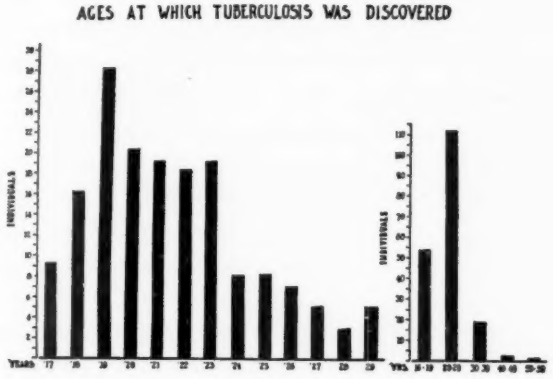

CHART 1

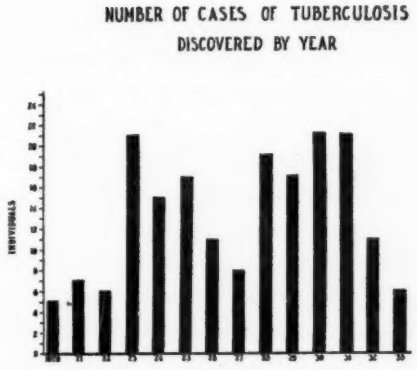

CHART 2

seem probable that two cases arose from the same source. In another university on the Pacific Coast, 5 active cases of tuberculosis occurred in one house group in one year. It was there discovered that one of the cooks had advanced pulmonary tuberculosis. Such a high incidence of infection in any social group has never been recognized at the University of California, nor has one case apparently been responsible for a second

case. In two instances, a brother and a sister developed signs of tuberculosis at about the same time. The two cases arising from the same source were sisters who probably contracted their infection from their mother.

It is greatly to the advantage of the student and to the interest of the University that illness be discovered as early as possible. This is especially true of tuberculosis. Eleven cases were discovered at the entrance examination and at least 39 more suspected. In the suspected cases, diagnosis was confirmed early during the first term of residence. Eighty-eight were discovered to have tuberculosis before they had completed their first year of work, 31 during the second year, 25 during the third year and 13 during the fourth year. Seventeen cases were discovered during the fifth year of residence, which normally is the first year in the graduate school. The comparatively large number in this group may, in part, be the result of the health examination required for advancement to professional courses.

The infection was discovered in 49 students as the result of some required physical examination. Local physicians reported 4 cases. The largest number, 130, presented themselves for examination on account of symptoms. Tuberculosis is frequently the subject of a lecture or reading assignment in courses in Hygiene, and the interest aroused leads students to ask for a chest examination. Although hundreds of such examinations have been made, the records do not show one that has revealed an active infection.

The presenting symptom most frequently leading to the discovery of an active case is chest-pain. Following, in order of frequency, are colds, cough, fatigue, haemorrhage, fever, loss of weight and nervousness.

A tabulation of all symptoms recorded for all the cases studied, shows chest-pain and fatigue, which here includes loss of vigor and strength, to be the two symptoms most frequently reported. Cough, colds, loss of weight, night-sweats, productive cough and amenorrhoea were reported in frequencies decreasing in the order of enumeration. Fever was seldom a complaint, but in 128 cases an elevation of temperature above 99° was found at the first, or on early examination.

Listing, in order of frequency, the symptoms reported by 1,499 women who entered a sanatorium during fifteen years, Williams and Hill (1) rank cough first, and pain in the chest eighth. Among the students, chest-pain assumes first place as a presenting symptom, and competes with fatigue, loss of strength and vigor for second place in all symptoms

recorded. Although cough is a frequent complaint, it is interesting that many students with active tuberculosis say they do not cough, and many who have been observed for long periods in the hospital do not cough.

Malnutrition is considered both a predisposing cause of tuberculosis and a result of the disease. (Chart 3.) There seems to be a very definite relationship between weight and tuberculous activity in the student group. At the time of the entrance examination, 75 per cent of those later found to have an active infection were below the weight expected for their age and height, whereas only 63 per cent of all students weighed less than the average. The 0 to −10 pound weight-deviation group, contains the largest number of all students, whereas the −10 to −20

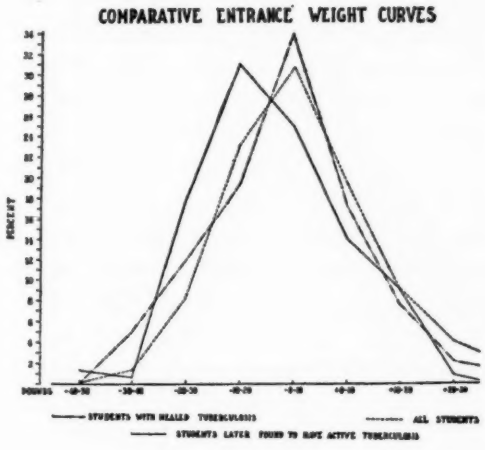

CHART 3

pound weight-deviation group contains the largest number of students who later were found to have tuberculosis. The histories and findings of 200 students who have had lymph-node or pulmonary tuberculosis, but for whom activity during their residence in the University could not be proved have been studied. Their weight-curve differed only slightly from that of the normal student group.

In selecting the 187 cases here presented from the many for whom tuberculosis was considered in a differential diagnosis, one or more of the criteria suggested by Brown (2) were used: "(1) The finding of tubercle bacilli in the sputum; (2) râles above the third rib or vertebral body; (3) X-ray evidence of a tuberculous lesion; (4) pleurisy with effusion; (5) haemoptysis of a dram or more." It was also remembered that "for

the diagnosis of the disease, the localizing symptoms far outweigh the general symptoms, but for the diagnosis of activity the general symptoms are vastly more significant."

For the localization of the lesion, greatest dependence is placed on the X-ray findings. Thirty-six showed a lesion of the left lung only, sixty-six a right sided lesion and seventy a bilateral involvement. There were 16 cases of pleurisy with effusion, and 16 individuals had one or more cavities. In a number of instances, when the X-ray was reported as

TABLE 1

Diagnoses

	MADE AT ENTRANCE	SHOULD HAVE BEEN MADE AT ENTRANCE	TOTAL
History of tuberculosis	11	5	16
History of pleurisy	10	18	28
History of glands	1	5	6
History of contact	0	21	21
Underweight	0	8	8
Chest findings	15	5	20
Sub-total	37	62	99
	PROMPT	DELAYED	TOTAL
Following symptoms	38		38
Following routine examination	4		4
Following contact	1		1
Lack of routine intradermal and X-ray		35	35
Negative X-ray findings		6	6
Made by other agencies		4	4
Sub-total	43	45	88
Total	80	107	187

negative, the diagnosis of active tuberculosis was made upon chest findings combined with symptoms. The histories of 6 such cases are included because early subsequent histories of the patients confirmed the diagnosis of tuberculosis.

Of the 187 cases, 80 were probably diagnosed promptly, but for 107 the diagnoses should have been made more promptly than they were, and most might have been made at the time of entrance to the University. (Table 1.) Of the diagnoses made at the time of the entrance examinations, or suggested by the entrance histories or findings, fifteen were

made on physical findings only. Eleven were suggested by previous histories of tuberculosis, ten by histories of pleurisy, and one by a history of cervical lymphadenitis. If all of the cases giving a history of tuberculosis, pleurisy and of lymphadenitis had been promptly and carefully studied, 28 diagnoses could have been made earlier. A more carefully planned history and physical examination should have transferred at least 5 diagnoses from the category of delayed to that of prompt detection. Twenty-one students, whose tuberculosis should have been found more promptly than it was, gave a history of family contact. Eight students, who at the time of their entrance examinations were more than 20 pounds underweight, were later found to have active tuberculosis.

If, since 1920, all contacts had been followed, if all those giving histories suggestive of tuberculosis had been selected for special study, and if all those markedly underweight had been looked upon as tuberculous until proved not so, then sixty-two more of the 187 diagnoses might have been made at, or shortly following, registration. The number of additional diagnoses is problematic.

It would be interesting and encouraging, to know in detail the subsequent histories of the individuals, who as students had tuberculosis. It has not been found possible to keep in touch with all of them. One hundred and fifty-nine left the University promptly following the diagnosis. Fifty-seven are known to have gone to sanatoria. Sixty-four of those taking a leave of absence later returned to continue their studies. Thirty-one continued as students to complete at least one term of work after a diagnosis had been made. The present state of health of sixty-eight is unknown; seventy-five are, or were recently, well. Twenty-five are still ill. Many of these have good prospects of a satisfactory arrest of their disease. Twelve have appeared to do well and have later suffered a relapse. Most of those attempted to return to the University to continue the cure and progress with their education. This is unsafe and seldom satisfactory. Ten of the number that it has been possible to follow have died. One student with health, family and financial difficulties committed suicide.

Of the number who established a satisfactory arrest of their tuberculosis, many live active lives. Three are known to be social workers, six nurses, four librarians, one dentist, one lawyer and five physicians.

In August, when 1,200 to 1,300 women students enter the University for the first time, tuberculosis comes with them. When the entire University family is assembled, tuberculosis is in its midst. How many

of this number have ever had experience with this infection, how many have had both the primary and adult reinfection types of infection, and for how many is the disease active at the monent? These are questions that cannot be answered accurately at present. We can, however, make an approximate estimation from the experience of others and from limited experiences of our own.

In other student groups we find great variation in the percentage incidence of tuberculosis. Yale reports 0.8 per cent in 1930 and 0.2 percent in 1931. At the University of Pennsylvania, 3.6 per cent of the students show X-ray evidence of apical lesions (3).

In 1933 X-ray pictures were taken of the chests of 467 of the 5,560 women students of the University of California. Approximately one student in every eight, or one-twelfth of all the students, had chest pictures during that year. A combination of the clinical and the X-ray evidence justified the diagnosis of healed tuberculosis in 69 cases, and of active tuberculosis in 9 cases. If we assume that all students who had, or had had tuberculosis, were X-rayed, then the incidence of active tuberculosis was 0.16 per cent, and of healed or arrested tuberculosis was 1.2 per cent. If, on the other hand, we assume that the 467 represent a random sample and that, among those who were not X-rayed, as much infection exists as among those X-rayed, the incidence of active tuberculosis was approximately 2 per cent and of arrested tuberculosis 15 per cent. Needless to say, neither assumption is correct, but we are fairly safe in concluding that for 1933 we had an incidence of active tuberculosis less than 2 per cent and greater than 0.16 per cent, and of arrested tuberculosis less than 15 per cent and greater than 1.2 per cent.

In 1931 2,500 students entering the University of Minnesota were given tuberculin tests and those who reacted positively had chest X-rays. In this way, one case far advanced, 5 cases moderately advanced and 9 cases of early tuberculosis were discovered: in all, 15 cases, or 0.6 per cent of the total number. In discussing the advantage of this type of examination, Diehl (4) says, "Had we depended upon physical examinations and histories for ordering X-rays of the chest, ten of the 15 cases would have been missed." Since this has been and still is to a large extent the basis of ordering chest X-rays for University of California students, we probably have missed two-thirds of the tuberculosis in our midst. Had the Minnesota method been used, not only should the 187 cases have been found much earlier, but in addition twice that number, or 567 cases, should have been found in the fourteen years. This would

be at the rate of 40.5 cases a year, and give a percentage incidence of 0.7 per cent which compares well with the 0.6 per cent for Minnesota students.

The Committee on Tuberculosis of the American Student Health Association (5) recommends as methods for the detection of tuberculosis:

1: A complete history.
2: A physical examination including auscultation of the bared chest for râles occurring during inspiration after the expiratory cough.
3: Routine intracutaneous tuberculin tests, with repeated tests on negative reactors at least each year.
4: Routine flat X-ray films of the chest of all new students as a matter of record, with stereoscopic films of all diagnosed as suspicious by flat films. X-rays on all individuals who change from negative to positive reactors.

When it is possible to carry out this program the questions which now cannot be answered will find their answer. Tuberculosis will be discovered in its early stages for students. There will then be much less loss of time and expense to the individuals and to society from the disease and a considerable number of lives will be saved.

To participate in such a program, will then be an integral part of each student's education. Although the proposed program is both expensive and exacting, it should be instituted and carried out in student-health services.

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ADMINISTRATIVE PROBLEMS IN THE CASE-FINDING OF TUBERCULOSIS

Routine Tuberculin-Testing of School Children with X-Rays of Positive Reactors[1, 2]

ETHEL D. OWEN

Attempts at case-finding in large cities were begun as early as 1889, when the Health Commissioner of New York City requested Hermann Biggs to outline a program. In many essentials the general outline is still followed. The first proviso for the campaign was the education of the public. In 1887, Sir Robert Philip in Edinburgh had approached the problem from a somewhat different angle, stressing chiefly the necessity of viewing this disease as a group problem.

In San Francisco we attempted to utilize all the past work done in the city. Since 1927, a program of case-finding has been carried out in San Francisco's public schools under the auspices of the Department of Public Health and the local Tuberculosis Association. In the fall of 1927, the State Tuberculosis Association visited San Francisco, and in selected schools took X-rays of all high-school children whose parents consented. The examination consisted of an X-ray, history and routine stethoscopic examination. From this time on, attendance at the local chest clinics increased markedly, so that at the end of a six-year period the number attending has doubled. In 1926 the total number attending chest clinics was 6,731 and in 1932 it was 13,074. Associated with this increase in attendance there has been a steady decrease in the incidence of the disease in the city. Doctor Lloyd B. Dickey of Stanford University had, prior to this time, conducted a series of tuberculin tests on children who came to the Stanford Out-Patient Clinics. This work covered a period of from 1925 to 1928. Dr. Dickey found the incidence of positive reactors among children of this group to be 45 per cent.

Therefore, with a considerable amount of work behind us, we launched an intensive case-finding program in the fall term of 1932. Our object

[1] From the San Francisco Department of Public Health, J. C. Geiger, Director.

[2] Presented at a meeting of the California State Tuberculosis Association, Fresno, California, April, 1934.

was case-finding primarily as a public-health measure: second, the education of the public. First of all, let me assure you that we recognize our limitations. No work of a frankly experimental nature will ever be tolerated by a department of health. Research must be carried on, but it cannot be done in public schools. It has taken years to build up an almost perfect confidence between the public and the health department. The relationship cannot be jeopardized. The public must in every instance be made to realize that no harm will come to children examined, and that they will be given information in simple terms regarding results.

We have a school population in San Francisco of approximately 100,000 children. The department of health has for many years carried on a routine physical examination of children from the preschool through the high-school age. Active cases of adult type tuberculosis are found every year in the course of the routine physical examinations.

Our supply of doctors, nurses and money is totally inadequate to meet the entire situation. Therefore it was necessary for us to begin in those schools where we knew in advance that we could find the largest number of contact cases. Following the example of Eastern cities where this work has been done, we chose three age-groups; first and most important, the 'teen age-group in high- and junior high-schools; second, a smaller elementary group, and a third, an even smaller preschool group. The criticism has been made that the existing chest clinics are adequate in their follow-up of contacts. Excellent as they are, this is not true. There are many undiagnosed cases of active tuberculosis in our city, cases unreported by private physicians, and "cultists" suffering from the disease, but denying its existence. In selected schools with three different age-groups, but with chief emphasis on the 'teen age, we began our routine tuberculin testing. First, our educational campaign had to be begun with the school authorities. Two doctors gave simple talks outlining what we proposed to do. We attempted to enlist the enthusiasm and coöperation of the school authorities. Without it, no health work can succeed. We were less fortunate in attempting to reach parents in P. T. A. groups. In the very schools we chose, the P. T. A. groups were poorly attended. Most of the parents worked, and many were foreign. A few talks were given to parents, but on the whole this was not considered very successful. Popular assembly talks were given to the school children themselves. This we felt was our best method of approach. In the 'teen age, the adolescent decides things for himself. At least this is the practice in San Francisco. Consent slips were made out on the

same general plan as consent slips for the Schick test with which parents have been familiar for the past decade. These consent slips were printed in Italian, English, Chinese and Spanish.

For a year in the health-school group, one of the doctors had done a Moro test. Forty per cent of children tested in this elementary health school, the *Buena Vista*, were positive. These children were practically all known contacts. We decided against the Moro test because it is not delicate enough and also because we found that the largest number of those parents refusing to give consent to the test did not do so because of the hypodermic needle.

The dilution of the O.T. was next considered. Again this group is requested to remember that we are dealing with a public who did not ask us to do the work. We realize that neither the parents, the children nor the school authorities would allow us to follow the sound clinical procedure of repeated tests upon negative reactors. This meant that we were to have one test. That test must be at best a screening-out test. It must be strong enough to uncover an active case of childhood-type tuberculosis, but not strong enough to give a slough, if the case happened to be active. The pediatricians of the two universites were consulted. The safe dilution was considered to be 1:1,000 O.T. It is prepared freshly every fourteen days at the University of California laboratories. The National Tuberculosis Association states in its 1933 publication on *Procedure in Case-Finding in Children*, "Re-testing of negative reactors may not be justified by circumstances where large numbers are involved."

Our statistics are complete only up until the end of 1933: out of 4,300 O.T. intracutaneous (Mantoux) tests there have been only ten sloughs and these have rapidly abated: one bad slough, one unfavorable newspaper story, and our whole program would be jeopardized. We fully realize that in certain Eastern cities, Opie and McPhedran have successfully used dilutions of 1:100 in school children. We did not feel that San Francisco was yet ready for such a strong dilution. We are neither practising medicine nor doing research work, *per se*. We can safely leave both of these endeavors to our well-equipped physicians, clinics and universities. That we have given an opportunity for treatment, advice and research I think we may safely state, since our day-by-day records in the Health Department show that during the past year 18,000 school children have been referred to private physicians and 16,000 (approximately) have been sent to clinics, because they were unable to meet

physicians' fees. Please note that very few, if any of them, would have gone voluntarily to physicians or health agencies.

After a scant two years of this work we cannot make any accurate statement regarding the fate of the negative reactors nor can we present accurately a study of the actual dates of infection. Any interested group of pediatricians by repeating the test every six months on their private patients throughout the child's school life could show an interesting record: namely the fact of infection together with the dates. It may be that in time we may be able to have annual tuberculin testing in all school children, repeating the test from year to year on negative reactors; but, since at present we have not personnel enough even to do physical examinations in the schools except in alternate grades, it is somewhat doubtful whether or not such a program can be arranged.

Approximately 48 per cent of the consent slips given out are not returned, or are returned with refusals. Only a relatively small number take the trouble to refuse and these refusals fall into three groups: (1) The "cultists"; (2) those families in which tuberculosis exists and they fear to have it known; and (3) when the family physician advises against it on the score that it is "unnecessary." The doctor's usual objection is that physical signs are lacking. The great majority of consent slips unreturned never reach the home at all. The adolescent decides against the test and relegates the slip to the waste basket. However, out of 9,998 consent slips given out, 4,696, or 47 per cent, were returned with consents, 1,852, or 19 per cent, were returned with refusals, and 3,450 or 34 per cent, were not returned at all.

The intracutaneous (1:1000) test is done by the two clinicians from the San Francisco Tuberculosis Association. The physicians usually can do from 100 to 150 in a school morning. The readings are done at forty-eight hours by the same physicians. The readings are done by the McPhedran oedema scale, listed as 1-plus, 2-plus, 3-plus and 4-plus.

Every parent who has consented to the test must be informed in simple language as soon as possible after the results are known. Therefore a form letter is sent to the parents.

Those upon whom a negative result was obtained are told that the test is negative: that it merely means that at this time the child is not suffering from a demonstrable tuberculous infection. The parent is warned that this does not constitute a permanent immunity and he is instructed regarding contacts.

Form-letters explaining the necessity for an X-ray are sent to the parents of those reacting positively. An attempt is made to explain the significance of the test. The parent is told that the positive reaction does not mean that the child has tuberculosis or will necessarily ever have it, but he is told that an X-ray is indicated. When the parent is able to pay for an X-ray he is referred to his own physician. A very large percentage of positive reactors are found to be on city relief. X-rays were taken as soon as possible, beginning with the 4-plus, 3-plus and 2-plus reactors. The greater number were taken at the San Francisco Chest Clinic. After the X-rays were taken, the clinicians read the films and tentatively classified them according to McPhedran chest charts, as outlined in the *Annals of Roentgenology* by L. R. Sante, 1933.

To quote from *The Chest in Children*, by E. Gordon Stoloff, 1933, "The x-ray is a diagnostic adjunct. To properly interpret these however, a knowledge of the clinical history and course is as essential and vital as is the evaluation of percussion and auscultation."

The classifications were (1) adult or childhood-type, active; (2) tracheobronchial lymph nodes partially calcified; (3) tracheobronchial lymph nodes calcified; (4) tracheobronchial lymph nodes partially calcified with healed parenchymal focus; and (5) suspected childhood-type tuberculosis.

Into the last group we arbitrarily place those films which appeared to be entirely negative, but in which the child had responded with a 3-plus tuberculin reaction.

From the viewpoint of the public, who buy our seals, one of the greatest defects in our surveys in the past has been that we did not put into practical use the information gained.

Arbitrarily, therefore, we attempted to make a classification of these children in order to facilitate the follow-up work in the schools. The physicians have a conference with the parent and the child on Saturday mornings. The result of the tuberculin test, the X-ray with its reading, a complete history and a careful chest examination result in a final classification. The frankly active cases, whether of childhood or adult type, are removed from school and hospitalized whenever possible: there are 32 in this group. We examine from 36 to 60 persons every Saturday morning. We have a fluoroscopic examination of contacts.

Into class 3 of our arbitrary grouping we place the suspects. Children in this group are given rest instead of gymnasium with a modified scholastic

program, instruction in health habits, a weight-chart and a four-hourly temperature record in school. In this group there are 265.

In group 2 are placed those with the lesser signs. This group may take regular work, but are not to engage in competitive games and are to have yearly physical examinations. There are 227 in this group.

Into class 1 are placed those with well-calcified lesions who give evidence of being in good health. In this group the same effort is made to find the source of the infection. This class-1 group is unrestricted in activity. There are 300 in this group.

At the beginning of the next year, all these children are seen again for reclassification. This is very important because, with gain in weight and a return to normal temperature, a less rigid regimen may be considered within the year.

Temperature and weight records were kept in school by the school nurse on a group of suspects. Obviously many of these children should not be in school, but they are better off there than in the squalid homes from which they come. Hetherington says, "Provision should be made in the high-schools for the prophylactic care of children who have advanced latent tuberculous infection that has not impaired their health; this may be accomplished by a modified school regimen that will avoid mental and physical fatigue and will provide adequate rest and nourishment."

Our statistics are as follows:

O.T. tests done	4,300		
O.T. positive	1,533 or 36	per cent	
O.T. negative	2,635 or 61	per cent	
O.T. not read	132 or 3	per cent	(These children were either not at school on the days of reading or they had moved away.)

The degree of positiveness

Total number of positive	1,533	
1 plus	520 or 34.0	per cent
2 plus	584 or 38.0	per cent
3 plus	439 or 27.0	per cent
4 plus	10 or 0.5	per cent

Final classification

Active tuberculosis	32
1. Hospitalized	17
2. Awaiting hospitalization	14
3. Died	1

Under school observation are 492. This number represents those falling into our arbitrary groups of classes 2 and 3: in other words, those suspected cases in which infection is probably still going on.

The age-incidence again confirmed the findings of other investigators, namely, that girls were infected about two and a half times as frequently as boys. The greatest age-incidence in our series fell between the years of 10 and 14 years. At over 15 years the incidence of infection in girls was still more marked than in boys, but the difference between the two was less marked.

The things accomplished have been: (a) The removal of 32 cases of active pulmonary tuberculosis from the schools within a two-year period. Fourteen of these would not have been discovered without this type of procedure. (b) The close continued medical school supervision of 492 children with positive tuberculin tests and suggestive X-rays and symptoms. (c) The education of 4,200 parents who gave their consents to the test. (d) The placing of a relatively large number of contacts under medical supervision. Many of the contacts were undoubtedly the source of the infection in the children examined. The number of these sources of infection cannot be accurately given at this time, but, three months ago, eighteen had been discovered. (e) The finding of a certain number of cardiac cases.

The weak points are: (1) The impossibility of giving school children rest in San Francisco because of inadequate facilities. (2) The difficulty of discovering the source of infection. In spite of the fact that in our Saturday morning conference we question and examine as many members of the family as possible, we are usually unable to get all of them. (3) The lack of a sufficient number of school nurses. (4) Unreported active cases of tuberculosis in the city.

A better program for the future would include a tuberculin test every year for every school child and the active coöperation of practising pediatricians in fixing the fact and the actual date of infection in the children in their practices.

HOW TO DETERMINE THE EMPHASIS OF A COMMUNITY TUBERCULOSIS PROGRAM[1]

BLEECKER MARQUETTE[2]

If ever there was a time when health-workers needed to know where they are going, that time is here. The period of easy-come, easy-go in financing has passed. The public is in a critical frame of mind and we need to examine every phase of our programs with detached, and even brutal, frankness. What is vital and productive must remain, but what cannot meet this criterion must go.

Obviously, the present general economic situation is a factor in determining for us somewhat the direction of our emphasis in tuberculosis work. Common sense and a clear picture of all the ramifications of the situation are fundamental. Though many of our communities to-day fall far short of providing adequate sanatorium accommodations, this is scarcely the time to launch ambitious programs in that field. The community, which did not realize its needs in this direction in palmier days and did not put forth every effort to build a satisfactory sanatorium program, lost a great opportunity. It will now have to bide its time until conditions are more propitious. It can utilize this as a time for planning for better facilities but scarcely as the time to execute those plans.

The great challenge that we now face is watching every phase of the machinery that we have built up, holding on to what we have and pushing forward in such directions as existing conditions will permit. Our problem is not unlike that of a military campaign. We must recognize where the enemy is, what plans of attack are likely to be most successful, arrange our forces in battle-formation, make our advances with intelligent knowledge as to the strategic time to advance, marshal reinforcements to strengthen our weakest points, and at times be content to devote our efforts energetically to holding the line. Our immediate task in most communities to-day is to determine the vital sectors and then to fight to hold those sectors.

[1] Read at a session of the Sociological Section of the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 15, 1934.

[2] Executive Secretary, Cincinnati Public Health Federation and Cincinnati Anti-Tuberculosis League.

Some Fundamentals

We must recognize the fundamentals and "major" on them. After all, the tubercle bacillus is the great enemy. Our chief concern must be to safeguard our facilities that prevent this enemy from attacking new victims. Isolation of those with active tuberculosis, keeping children away from the active case, safeguarding those who have been contacts, prompt reporting, early diagnosis, follow-up on discharged patients to prevent breakdown, are objectives that must have priority.

We must stand back of our health departments; we must maintain our sanatoria at a high point of efficiency; we must keep our clinic and nursing facilities going. These are absolute essentials. If to see them thrive we have to do a somewhat less vigorous educational job or let down somewhat on our rehabilitation work or our summer camps, we are choosing the lesser of two evils. Naturally we shall fight to hold our programs intact, but if conditions beyond our control force a retreat on some sectors we must choose those sectors with discrimination.

Appraising Tuberculosis Work

Perhaps the best general aid in deciding how best to direct our efforts is the appraisal evaluation of tuberculosis activities first presented by Dr. W. F. Walker at our 1932 conference and later in somewhat modified form by Dr. Carl E. Buck of the American Public Health Association at our 1933 meeting. This plan aims to assist any community in appraising its general tuberculosis program and by the method of scoring to determine in what respects the program is strong and in what respects it is weak. As Dr. Buck pointed out in his address, it is a community tuberculosis program appraisal, but it can and should be used to show what agencies are engaged in the program and to what extent each agency is rendering service in accordance with the needs of the community. It is not claimed that this exact appraisal form is in all respects satisfactory. The form is, as you know, being carefully studied by the National Tuberculosis Association and will be made available as revised in the near future.

The appraisal method is not proof against misuses by way of padding figures, it does not measure quality of the work, and it does not tell the whole story. Obviously any intelligent executive will realize that there is no advantage to be gained by deceiving himself or his community as to the real facts. The value of this measuring rod will be determined by

the honesty with which it is used. It must be supplemented by an intelligent and accurate knowledge of the community's program. The scoring helps to give a general picture of what is being accomplished in the six major fields of tuberculosis work: namely, (1) general health education; (2) nursing; (3) institutional care; (4) clinic facilities; (5) case-finding; and (6) postsanatorium care and rehabilitation. If we rate low in any of these fields we have some tangible points for study and action. Obviously, we have to determine our emphasis in the light of what we have a chance to accomplish. It may be that reduced funds will make it necessary for some of us to fight hard even to hold the vital parts of our present program. Yet it is a time for careful analysis and for planning for the future.

One Evaluation of Tuberculosis Work

It may be helpful to cite the results of one appraisal study in which this method of scoring was used. The exact score received is not important except that it was not high, although much excellent work was being done. The weak points were brought out in clear relief and this in turn led to a careful study of the whole program including quality as well as quantity. Certain fundamental weaknesses in the general set-up were shown. No doubt many of these weaknesses were known, but the value of the study was to point them out unmistakably and to outline definite ways and means of overcoming the weaknesses. Here are some of the major recommendations that were made:

1: A full-time trained health-officer.
2: A completely different arrangement for sanatorium care to replace decidedly inadequate facilities in an old institution in bad repair, without X-ray or dental service, without sufficient provision for children, without a consulting service,—a place caring almost entirely for patients in the advanced stages of the disease.
3: Applying the health-education program more specifically to the racial and age-groups in which the tuberculosis problem is outstanding.
4: A revised clinic service planned to utilize fully such clinic aids as X-ray and sputum tests to find more early cases.

Clearly these recommendations were based upon more than a mere scoring, but the scoring definitely served to point the way to an intelligent study based upon the scoring, which in turn led directly to these recommendations. Certainly this community now knows much better than do most of us where to place the emphasis in its future program.

Results of a Health Appraisal in Cincinnati

Cincinnati has had some encouraging experience with appraisal methods. In 1926 a health appraisal of Cincinnati was made by the American Public Health Association at the request of the Public Health Federation. Our scoring for tuberculosis control—only 48 per cent of the possible total—proved the least satisfactory among our health services. The recommendations made proved fruitful. Since that time marked progress has been made by the Health Department, the Anti-Tuberculosis League and other organizations in strengthening our tuberculosis program. The tuberculosis-sanatorium extension and rebuilding program was already under way. This program resulted in completely modernizing the institution and in increasing the total number of beds available for active tuberculosis cases from 296 to 535 (considerably more than one bed per annual death) and in the construction of an excellent preventorium providing for 100 children. Instead of an outworn institution we have an excellent sanatorium which is, we feel, a credit to our community.

A new summer camp for colored children has been constructed and put into operation. A diagnostic tuberculosis clinic has been added at the out-patient dispensary of the General Hospital. Better social-service care for tuberculosis families has been provided by the Department of Public Welfare and our social agencies. The Health Department has secured an X-ray unit for its clinic, with the result that the number of cases of tuberculosis discovered there doubled from 1931 to 1933. The percentage of incipient cases found increased from 20 to 29 per cent. The percentage of advanced cases decreased from 50 to 19 per cent. Through the coöperation of the tuberculosis-sanatorium staff and the Department of Health a consultation service has been developed, available to practising physicians and to the district physicians employed by the Board of Health. While we have more than one bed for each death at the present time the facilities are far from adequate, there being a constant waiting-list of about 50 patients for the sanatorium proper and 25 children for the preventorium. This has demonstrated the importance of developing as effective a program as is possible for patients who have to be cared for in their homes. Such a plan has been worked out and is functioning through the coöperation of the tuberculosis-sanatorium staff and the Health Department.

The Health Department is making a special study of negro children in one of our schools, using the X-ray and the tuberculin test. The Shoe-

maker Clinic, devoted to the care of negro patients, developed a special tuberculosis service with members of the staff of the sanatorium as the clinicians. Here negro physicians are given opportunity for training in diagnosis.

The Anti-Tuberculosis League has organized the Negro Women's Health Club plan, in which some 2,000 women of the great congested area of the city have been enrolled; other groups have been formed in the outlying negro areas. These families are taught the fundamentals of personal hygiene. Since 1926, 2,707 of the members of these families have been taken to the Health Department Clinic for physical examination and 232 have been reëxamined; 21 active and 55 suspicious cases have been found.

Not all of these advances have been due to the appraisal, but it did help us to see our problem more clearly and served to challenge us to meet this problem. This particular study included the general field of health work and many other changes have resulted from it, but this is not the place to discuss the general health program.

Testing Appraisal Results

There are many searching questions that we need to ask ourselves in connection with the appraisal to secure full value from it. In the field of health education, if our scoring is creditable, is the quality of the education work all that it might be? Is it reaching the groups among whom the tuberculosis death-rate is highest? Is it being pushed vigorously? Are we modifying our programs and injecting new ideas and new methods? To what extent has our community really been educated to the point where they know the things that we consider fundamental in tuberculosis? Can we count on vigorous public support to prevent drastic reduction in public expenditures for tuberculosis work?

In reporting, we need to know whether effective use is being made of the reports. What follow-up is there to see that the cases are being satisfactorily cared for and contacts protected? Are physicians being notified when they fail to report their cases or when the first notice comes with the death-certificate? Of what value is reporting and how long will good reporting continue if we do nothing about it?

As to the clinic set-up, is the equipment modern and is the quality of the work good? Are we finding a sufficient number of minimal cases? Are contacts being rigorously examined and followed up? Are we examining enough people in the age-groups 20 to 45? Are the clinics located to the best advantage? If our community has several, are they properly

integrated? Are the reports on clinic work assembled and made available at any one central point so that we can at any time get a picture of the total amount of work and how it varies from year to year and month to month?

As to our sanatorium facilities is there a high standard of administration? Is it adequate in size and modern in equipment? Is the staff competent and is the morale good? Does the quality of the food served hold up? Are patients willing to go to the sanatorium? Is the staff of the sanatorium being used to the best advantage in the community program? Is there an adequate and competent consultant staff? What percentages of the cases are minimal, moderately advanced, advanced?

If we have summer camps are they intelligently conducted as health camps with the emphasis on the fundamentals and not on the frills? Is there an adequate follow-up on the children throughout the year? Are we sure that we are selecting for our camps the children who need this service most? Are we studying our results with sufficient care?

In nursing service, we need to inquire: Is there among the nurses an intelligent understanding of the best approach and a real enthusiasm for tuberculosis work? Is the coöperation with the medical profession satisfactory, so that it welcomes the service of the nurse, and, if not, whose fault is it?

Capitalizing on Mortality Studies

Mortality data are helpful in determining where to "major" in our tuberculosis programs. We already know that the tuberculosis death-rate is high generally among men of middle age in industry, among adolescent girls and among the negro population. Obviously if this is true in our own community, as it probably is, we need carefully to examine our programs to determine whether we are placing sufficient emphasis on our programs for these groups.

The availability of population statistics by census tracts in many of our large cities is making it possible to get a more accurate picture of our problem. We can now determine where, in our city, death-rates are highest and can correlate the tuberculosis death-rate with economic status and many other factors. We can determine whether case-finding is satisfactory in our tracts of highest mortality and can "major" on emphasizing better case-finding and clinical facilities for these areas.

Cincinnati, through its Public Health Federation, is now completing, in coöperation with the Board of Health, detailed mortality studies for the 3-year period, 1929–1931, inclusive. These studies are being made in

two parts. Both studies are of resident death-rates by race- and age-groups for the principal causes of death. One study being made by Mr. Wm. S. Groom, a member of the Coördinating Committee of the Public Health Federation, compares Cincinnati with 13 large American cities considered to be fairly homogeneous in population. The other study, directed by Dr. Floyd P. Allen, Associate Secretary of the Federation, analyzes the mortality by census tracts and by economic areas of the city.

Here are very briefly some of the things we know about tuberculosis in Cincinnati to-day that we did not know before.

Comparison of 13 Cities

1. Cincinnati's death-rate from all forms of tuberculosis was higher for the three years studied than the weighed average of these 13 cities. It was slightly higher for whites and decidedly higher for negroes.

2. The net annual excess for the white population was 38. The white rate was below average in some age-groups and so little above in other age-groups as to have no significance. The excess occurs principally at ages 25 to 35 and 45 to 55.

3. The net annual excess for the negro population was 72, Cincinnati's rate being higher in each age-group though not significantly higher in several of these groups.

4. From all causes of death, Cincinnati has a net annual excess above the average mortality of these 13 cities, slight for the white but marked for the negro population. For the whites 43 per cent of this excess is due to tuberculosis; for the negroes 56 per cent is due to tuberculosis.

Census-Tract Studies

1. Our resident rate for tuberculosis, all forms, is 92.8 per 100,000 population, the white rate being 59, and the negro rate 388.5 or 6.4 times that of the white population.

2. In the census tracts in the lowest economic group (where the equivalent monthly rentals based on the 1930 Census ranged from $17.00 to $26.00) the tuberculosis death-rate was 191.8, the white rate 92.3, and the negro rate 500.8, (the negro rate being more than 5 times the white rate). In next to the highest economic tracts (equivalent monthly rentals $46 to $65) the tuberculosis rate was 55.7, with a white rate of 50.9 and a negro rate of 166.9. In this higher economic group the negro rate is about three times the white rate.

3. The tuberculosis rates for both the negro and the white population

are closely related to economic status, decreasing from the highest rate in the lowest economic status to the lowest rate in the highest economic status.

Time does not permit giving more than this very brief summary. It is sufficient to indicate that these studies are of great value in showing us the nature of our problem. Our rates are too high, especially among negroes, and presumably can be further reduced. We need to place still more emphasis on work with the negro. Our problem is chiefly concentrated in our lowest economic tracts and it is there that we must intensify our efforts.

Such studies as these should prove helpful to other communities in determining the emphasis in their programs. Cities which have their census data by tracts will benefit particularly. In 1940 a restudy will show more accurately than has been possible heretofore exactly what developments a decade brings.

Of course our mortality studies have included all major diseases. For some causes our rates are low; for others, average. We have learned that our rates for appendicitis, diarrhoea and enteritis, are high. Organized attacks on these causes of deaths are already under way. Scarlet fever, whooping-cough and automobile accidents take a higher toll than average. We are hopeful that this more accurate knowledge of our problem may make it possible to save lives now needlessly sacrificed.

Community Coöperation

The specialized tuberculosis program that we have been discussing cannot stand alone and be effective. We are involved in the general community-health problem. If there is neglect in the provision of medical care for children, if the school health program is weak, if adequate attention has not been given to the fundamentals of diet among the unemployed and dependent families, if we are losing out on nutrition, if housing conditions and overcrowding are constantly growing worse, if the material needs of families in which there has been or is tuberculosis are not being met on a satisfactory standard, then our progress is endangered. Tuberculosis executives must make it their business to see to it that they are in touch with these other features of the community-health program and, as they see gaps developing or retrogression setting in, they must put their shoulder to the wheel in coöperation with other health forces to lend such help as they can. In this crisis emphasis may well be placed upon securing close coöperation and the finest kind of understanding among those engaged in this great task of improving and safeguarding

the public health. This is certainly not the time for bickerings, jealousies or scrambling for credit. Health councils and federations have shown their value in the larger cities in bringing about the kind of working together that helps to produce well-rounded health programs vital to the effectiveness of every special field.

We are not in a static field: it is evolving, changing, growing. Never was there so great a possibility of still more rapid change. The executive, who is not alert to significant trends, new discoveries, or disproved methods, will soon be lost in the procession.

What the Future Holds

The very fact that the general mortality of the country has been relatively satisfactory and that the tuberculosis death-rate in particular has continued to decline may represent one of our greatest dangers. This fact is so striking that it is being called to the attention of the public and is resulting, as you know, in a feeling that all is well and that, perhaps, if the mortality remains perfectly satisfactory despite the depression, then need for public-health work may not be as great as we had pictured it. We do not know exactly what is happening to the general health and vitality of the population. It seems sensible to believe that the favorable mortality may very well be the result of the high standards of living that existed in the past, the striking progress of public-health activities, the absence of major epidemics. We are probably cashing in now on favorable conditions of the past. While conclusive evidence is lacking it is reasonable to expect that malnutrition may be on the increase, particularly in those families of the unemployed not receiving public support. There is evidence now that the extent of illness has increased among families who have dropped sharply in the economic scale. There are indications in many communities of a decrease in the correction of dental defects. Certainly a vast percentage of our people are undergoing mental anguish and suffering not experienced in years. Appropriations to health departments and to tuberculosis sanatoria are decreasing, and personnel is being dropped.

We well know that the results of the situation we are passing through may show up in later years in decreased vitality, which in turn may increase infant and tuberculosis mortality. No matter what the final outcome may be, certainly the most disastrous thing that could happen would be to have the public get into the frame of mind that we can afford to let down on the effectiveness of our public-health work. It is our responsibility to see to it that this does not happen.

DUST AND ITS RELATION TO TUBERCULOSIS[1]

JOHN B. HAWES, 2ND

In this discussion of dust and its relation to tuberculosis I shall confine my remarks to the so-called "harmless dusts," eliminating those which contain free silicon. The harmful effect on a tuberculous process of the inhalation of sand, granite and other dusts containing free silicon is generally acknowledged and needs no further comment. On the other hand, there is no such consensus of opinion in regard to the effect of the harmless organic and non-silicon-containing inorganic dusts on latent or quiescent tuberculosis. And yet this question is constantly arising in the courts and before industrial accident boards all over the country so that at present it constitutes a "racket" of no mean proportions.

Those dusts which are generally looked upon as harmless, as far as the lungs and tuberculosis are concerned, comprise (1) those of organic origin made up of the protein dusts some of which may occasionally cause asthma, hay fever or other anaphylactic phenomena and the carbohydrate dusts such as flour which presumably have no effect, specific, irritating or otherwise, and (2) the inorganic non-silicon-containing dusts including lime, marble, carbon and other elements. Talc, although a silicate, contains no free silicon and, along with other silicates with the exception of asbestos, is generally looked upon as harmless. At this point one might ask why if these dusts are harmless should they be a subject for discussion here and, likewise, why if harmless should they have any harmful effect on a tuberculous process, latent or even active. These are perfectly proper questions and, theoretically, have only one answer, namely, if a dust is really harmless it certainly will do no harm to a tuberculous individual. As Dr. Harry Bray of Ray Brook, New York, from whom I always expect to receive a frank answer to any question I ask him, says, "Harmless dusts are harmless until Doomsday notwithstanding statements to the contrary from Bostonians." Exactly why he picks on Boston I do not know. On the other hand, there are others who can speak with equal authority who feel differently in regard

[1] Read at a session of the Clinical Section at the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 15, 1934.

to this matter. Philip King Brown of San Francisco, for instance, states just as emphatically, "Harmless dusts are *not* harmless to a person who has quiescent tuberculosis," and backs up this statement with striking figures he has just sent me. In a survey of 756 cases of pulmonary tuberculosis in 27,000 admissions to the Southern Pacific Hospital during the past six years the general incidence of the disease was 2.7 per cent, varying from 0.84 per cent among engineers, brakemen and firemen to 3.9 per cent among car-cleaners and other dusty trades. Other authorities are of the opinion that in *normal* amounts these dusts are entirely innocuous but in *excessive* amounts so as to produce throat and bronchial irritations, thereby paving the way for intercurrent respiratory-tract infections, they are anything but harmless.

This whole subject is one of very real practical importance and one urgently in need of frank discussion and clarification. I should like to find adequate answers to the following questions but doubt very much if I shall.

1: Does exposure to harmless dust except in excessive amounts over a long time tend to reactivate a quiescent or dormant tuberculosis?
2: What constitutes dust "in excessive amounts?"
3: What is the effect of those organic protein dusts, cotton, wool, fur, flax, etc., which may cause allergic phenomena and of certain inorganic dusts which may cause bronchitis and throat irritations on a quiescent tuberculosis?
4: Are we justified in advising our tuberculous patients, as the vast majority of us do, not to go into a dusty occupation even if we know the dust is a harmless one?

During the past 15–20 years I have appeared many times before the Massachusetts Industrial Accident Board to testify in cases in which dust was involved. Our laws in Massachusetts in regard to what constitutes an industrial accident are very broad, perhaps too much so. A disease such as tuberculosis, for instance, if it can be proved to have arisen not only in the course of but *out of* a person's occupation constitutes an industrial accident and as such is compensable. Under this act, therefore, may come all sicknesses and diseases attributable to dust, including pneumonoconiosis, tuberculosis, bronchitis, asthma and others. While many of these claims arising out of a dust hazard, as in the case of granite-cutters, sandblasters, etc., are perfectly just and proper ones, there are many others, in fact, the majority, that have no sound or legitimate basis whatsoever. As I said before, this whole matter in Massachusetts

and, according to my friends, the same situation exists in other states, has developed into a very genuine "racket." The time seems to be approaching when the street-cleaner, the ashman and coal-driver will claim and sometimes obtain compensation for any disease of the lung or bronchi that happens to hit him in the course of his work. The insurance companies in Massachusetts have hundreds of such cases every year, and as each case over and above any compensation which may be awarded costs at least $500 it can readily be seen that in dollars and cents alone these dust claims amount to a very considerable sum, not including loss of time and energy. There are always plenty of lawyers, most of whom are sincere in their belief that their cause is a just one, who will gladly handle these cases; doctors abound who will testify for their patients that the dust to which they have been exposed was entirely responsible for their condition without having inspected the premises or really knowing the exact conditions under which the man worked. Physicians as a rule are only too willing to believe implicitly their patient's statement that the conditions as to dust under which he worked were intolerable, and will testify in court that in their opinion there was a direct causal relationship between the development into activity of the tuberculous process and the dust to which the claimant was exposed even if the dust was known to be a perfectly harmless one.

Naturally enough, the workman can look upon this subject from only one angle. He knows perfectly well that granite-cutters, sandblasters and many foundry-workers are constantly receiving compensation because of exposure to dust, either on the basis of pneumonoconiosis or that it reactivated an old tuberculosis. To the workman all dusts are alike and it is only human nature for him to claim similar compensation for himself under what he believes to be exactly similar circumstances. Often he wins his case. The Martin King case is a striking example of this. I was asked to see this man for an insurance company in January, 1927. I found him in an advanced stage of pulmonary tuberculosis. His occupation was that of a lumper and later driver on a coal-truck, loading and delivering soft coal for a Boston coal company. Although with a wife and children the situation was a pathetic one, I could see absolutely no causal relationship between his occupation and the development of his tuberculosis and so testified, knowing perfectly well that soft-coal dust was innocuous and that the incidence of tuberculosis of workers in soft coal was remarkably low. Nevertheless, the Industrial Accident Board awarded him, or rather, his widow a large sum in com-

pensation. In my files I have over 350 dust cases, most of which it is true are made up of sandblasters, granite-cutters or foundry-workers. In addition to these, however, are many records of men and women who have worked at almost every other kind of dusty trade, such as rubber, jewelry, printing, wood, leather, tobacco, lime, marble, wool, cotton, and others, in which dust of the "harmless" variety was present in varying amounts. With the exception of the stone-cutter, in each of these cases in which I have testified in addition to cross-questioning, examining and X-raying the claimant, I have insisted upon personally inspecting the plant where the work was carried on and, as far as possible, seeing the exact conditions under which the man worked and ascertaining the amount and the nature of the dust to which the worker was exposed. I have, therefore, a fairly intimate knowledge in regard to dust conditions as they exist in Massachusetts industries; but despite this fact I frankly admit that I have as yet failed to come to any definite conclusion as to whether or not the harmless dusts under certain conditions may or may not be harmful to a patient with latent tuberculosis.

The literature on this subject is to be found chiefly in the writings of workers and investigators in the field of industrial medicine. Voluminous as this literature is, it gives the physician who is interested in the problem of the individual patient rather than in that of industrial disease remarkably little help. From the purely clinical viewpoint as to the effect of these harmless dusts on a latent pulmonary tuberculosis one finds little or nothing. For instance, in a careful review of practically all the literature of this country and Europe of the past five years on this subject, I could find very little that was of genuine assistance. Occasionally, one met with a general statement such as the following by Sir Thomas Oliver, who says that "dust may do harm by locally predisposing the pulmonary soil for the reception of the tubercle bacillus as well as by reducing the general resistance of the individual." While this may be undoubtedly true, it is not specific enough to be of much help. Landis, who has very definite views on this subject, calls attention to the errors to be found in many of the statistics in that other factors are not taken into account. "It is essential," he writes, "that the effect of industrial hazards shall not be complicated by the influence of social and economic factors of a more general nature." For instance, the harm said to be done to the workers in the flax and carpet industry—which dusts are certainly harmless enough—comes from the silicon-containing, inorganic dust mixed with the wool or flax. One of the most marked

cases of pneumonoconiosis I ever saw was that of a worker in a chocolate factory! On investigation I found that for many years his sole job had been that of resurfacing the granite millstones by means of which the cocoa-bean was ground. Likewise, Landis points out that the high mortality from tuberculosis found in the tobacco industry does not come from the tobacco dust, because there is practically no such dust, but from the low wages and poor living conditions of the workers. But while Landis, in this article from which I have quoted and in a personal letter to me, is strongly of the opinion that in no case has it ever been shown that organic dust has done harm to the lung, he does admit that certain such dusts, as stated in the beginning of this article, may give rise to a protein intoxication such as asthma, etc., and that other dusts may be a source of danger as carriers of bacteria. Here again the physician dealing with tuberculosis would at once ask whether or not attacks of asthma or bronchitis caused by some presumably harmless dust might not reactivate a hitherto latent tuberculous process. This and other similar questions are important ones and should be answered as definitely as possible. Although there is bound to be differences of opinion I hope that some consensus of ideas can be agreed upon which will represent the opinion of the majority of those of us who are engaged in this work. I know that such an opinion would be of inestimable value to industrial accident boards, insurance companies and to physicians called upon to testify in such cases.

As I have said, a review of the literature on this subject gets one nowhere. The admirable work done by the physicians of the U. S. Public Health Service under Dr. A. E. Russell and others, embodied in the departmental bulletins, is thorough and painstaking, but fails to give evidence which will help to decide the individual case. In an investigation by this department, for instance, of workers in a textile plant, it was shown that 56 per cent of the illnesses were respiratory in nature in the way of colds, influenza and grippe, while the incidence of tuberculosis was very low; in another, that workers in soft-coal mining, cement, silverware, cotton and other textile industries and municipal street-cleaners likewise showed a markedly increased rate for colds and similar respiratory infections but a very low rate for tuberculosis. In England, Collis, who has done an immense amount of work on this subject, also points out the high rate for bronchitis and pneumonia and the low rate for tuberculosis in workers in cotton and wool, flour, leather and boot industries. He classifies all the calcium compounds, limestone, gypsum,

Portland cement, among the harmless dusts and makes the broad statement that organic dusts, as met with in industry, have *no* harmful effect on the lungs. Likewise, Russell in a detailed study on workers in a Portland cement plant found bronchitis very frequent and tuberculosis very rare. Of 570 men examined, only 21 were found with tuberculosis and only two with active disease, each of whom had had the disease prior to entering this work. Arrested cases apparently suffered no harmful effects. He found no case of tuberculosis that he could attribute to exposure to this harmless dust and no evidence of reactivation of a tuberculous process. Feil, in France, investigated a similar industry and and found likewise an increase in bronchitis but not in tuberculosis, and concluded that Portland cement dust does not predispose to tuberculosis while German investigators have apparently reached the same conclusion. A further review of the literature on this subject from other authorities in this country and in Europe might be given but is quite unnecessary. The evidence in regard to the effect of these harmless dusts on the health of the workers shows conclusively that there is a definite increase in acute respiratory infections, colds, grippe, influenza and bronchitis over the normal, but no increase in the incidence of tuberculosis. Indeed, in the case of the soft-coal and lime industries there seems to be even less tuberculosis than is found in the average industrial population. No other conclusion is possible.

But this is not the entire story by any means. So far we have been dealing with certain industries and the dusts involved therein. Now, let us turn to the individual case, that of a man who has an arrested or quiescent tuberculous process in his lungs of which he may or may not be aware. The question of his earning a living must come up. Is it safe for such a man to go into a dusty occupation even if the dust is a harmless one, and, should he break down and develop active disease, is a physician justified in testifying that this reactivation of his tuberculosis arose not only "in the course of" but "out of" his work? The crux of the situation lies in these two words, "out of." And again, if a man with a quiescent tuberculosis without knowing it, which for years has been compatible with perfect health and full working capacity on his part, breaks down at his work in which he has been exposed to one of these harmless dusts, are we justified in using a *post hoc, propter hoc* argument, and conclude that his relapse arose in the course of and out of his work? Also, are we physicians, whether specialists in the subject or general practitioners, doing the right thing in forbidding our patients to enter a

trade in which dust of any kind is involved or are we inflicting an unnecessary hardship in telling a man he cannot go back to his old job to which he is accustomed and at which he can earn his living simply because he will inhale a certain amount of harmless dust? There is practically nothing in the literature on which to base an answer to these questions. In an endeavor to formulate some kind of an opinion on this subject I wrote personal letters to a number of my friends, each a recognized authority in the field of tuberculosis and diseases of the lungs, asking three questions as follows:

1. Granted that the non-silicon-containing dusts are really harmless to the normal individual, are they harmless to the person with a quiescent or arrested tuberculosis?

The replies to this question were equally divided, one-half considering such dusts harmless to everyone, whether tuberculous or not, and the other half of the opinion that although harmless *per se*, by producing irritation to the bronchial tubes, the dust might give rise to bronchitis and other infections and so indirectly reactivate the tuberculous process. Drs. Harry Bray, Maurice Fishberg, H. R. M. Landis, Edgar Mayer, Paul McCain and J. A. Miller, for instance, consider such dusts harmless, while an equally authoritative group, such as Philip King Brown, C. Hartwell Cocke, H. L. Barnes, E. A. Locke, David Lyman, are of the opposite opinion. A few qualified their replies by stating that such dusts were harmless except in "excessive" amounts. This of course raises the question as to what constitutes "excessive" and will be considered later. A few brought up the interesting and important point that certain dusts harmless in themselves both to normal and to tuberculous individuals might and often do act as carriers of infection and thereby cause attacks of bronchitis, etc., and other upper-respiratory tract infections. Floyd of Boston told me that in his researches in street dust he found that in the summer months such dust was practically sterile but that similar dust collected during the winter months in New England at least contained many bacteria of various kinds. J. H. Elliott of Toronto confirms this and states that he considers street dust in fall, winter and spring a potential cause of respiratory infection and as such might do harm and was to be avoided. Philip King Brown likewise states most emphatically that he would not allow any tuberculous patient, no matter in how good condition, to go back to a job such as dusting and cleaning out sleeping-cars, not because such dust in itself is harmful but because of the organisms that go with it.

My next question was as follows:

2. Do you think that exposure to "harmless" dusts except in excessive amounts is a factor in reactivating quiescent or inactive tuberculosis?

The answer to this was overwhelmingly in the negative, only two out of the total number of men to whom I wrote being of the opinion that exposure to such dusts not only might reactivate a tuberculous process but might justly be looked upon as the causative factor in so doing. The remainder, many of whom by their answers to the first question apparently felt that such dusts might do a certain amount of harm to the tuberculous individual did not feel that it could be demonstrated or proved that this dust was the sole factor in causing the breakdown so as to merit compensation as an industrial accident. I am inclined to agree with this opinion.

My third question was one that concerns everyone who handles tuberculosis:

3. Would you allow a patient of yours with quiescent or arrested tuberculosis to take up any occupation in which he was exposed to dust, even if of the "harmless" variety?

Here again the great majority of my replies were to the effect that under no circumstances would they allow a patient to go into a dusty occupation regardless of the kind of dust. Two men, each from North Carolina, Dr. Paul Ringer of Asheville and Dr. Paul McCain of Sanatorium, were definitely in the affirmative. Three qualified their answers saying that unless the dust were excessive they would allow their patients to take up such work particularly if it was their old trade. The remainder were emphatically in the negative.

Here, too, arises the question as to what constitutes dust in excessive amounts. The authorities in industrial medicine, such as Philip Drinker of the Harvard School of Public Health and Bloomfield of the U. S. Public Health Service, feel that over 100 million particles per cubic foot which would cause a faint haze in the air and would constitute a "nuisance" would be excessive and should not be permitted. My own method of deciding this question, a crude one I admit, would be based on a personal inspection of the plant and of the exact work the man did, and by the use of my own common sense to come to a decision. I imagine that opinions might vary as much on this as on other matters connected with this subject.

Is it possible to arrive at any definite opinion from all this mass of material and opinions pro and con? I fear not, but I hope that by bringing it up for discussion a little of the dust—and it is not altogether a harmless dust—that surrounds this subject may be dispersed and the atmosphere cleared to some degree at least. I dislike "rackets" of all kinds and this "dust racket" is a most pernicious and far-reaching one. My own opinion has not been materially changed by my investigations. For the granite-cutter, the sandblaster and often the foundry-worker I will gladly testify that his tuberculosis arose not only *in the course of* but *out of* his work. But I firmly believe that the man who comes down with tuberculosis while working in a cotton or woolen mill, a wood-working shop or at a lime or coal industry, for instance, and who claims that his disease was caused by the dust to which he was exposed should not be awarded compensation unless working conditions as to dust were extraordinarily bad on this score. A personal inspection of the working conditions as to dust and other factors is essential in order to arrive at a just conclusion.

There is one point in regard to the protein organic dusts that should be considered. What is the effect of an acute attack of asthma or hay fever or asthmatic bronchitis brought on by exposure to wool, cotton, fur or some similar organic dust on quiescent tuberculosis? The only patient I can remember in whom this question arose was that of a young man with a very slight tuberculous process who went to work in a cotton-mill. Starting in the sorting-room, a very dusty place, he promptly came down with what the workers called "cotton fever," an acute bronchitis lasting a week or ten days. Apparently, it did him no harm. Thousands of tuberculous patients have their annual attack of hay fever and are none the worse for it as far as their tuberculosis is concerned and not a few have a combination of asthma and tuberculosis which in the experience of such men as Dr. Robert Cooke of New York and Dr. F. M. Rackemann of Boston does not seem to affect the tuberculous disease one way or the other. My own experience though limited as to this would be confirmatory.

In summarizing this extremely intangible subject I might well present my own answers to the questions I asked at the beginning as well as those I put up to my friends to whom I wrote and to whom I wish here to express my thanks for having given me the benefit of their experience on this subject.

1. I do not believe that exposure to these harmless dusts in normal amounts and under normal conditions will reactivate an arrested or quiescent tuber-

culous process. I do believe, however, that dust in excessive amounts under abnormal conditions, such as street dust in winter and fall or germ-laden dust from sleeping cars, etc., which might well cause irritation and infection of throat, trachea and bronchi, is a potential source of harm.

2. I do not believe that dust which may cause allergic phenomena, such as asthma, asthmatic bronchitis or hay fever, will reactivate or harm a tuberculous process.

3. As to allowing an arrested or quiescent tuberculous patient to take up a trade in which he would be exposed to a harmless dust, I admit that, as a result of my study on this subject, I have changed my opinion, so that at present I would be quite willing to allow my patients to take up such dusty work unless the conditions as to dust were *extremely bad*.

I wish to express my grateful appreciation to the following men who gave me the benefit of their opinion on this difficult subject:

Dr. Philip King Brown of San Francisco, California; Dr. David Lyman of Wallingford, Connecticut; Dr. A. E. Russell, Washington, D. C.; Dr. E. J. Murray, Lexington, Kentucky; Drs. Henry D. Chadwick, Cecil and Philip Drinker (Harvard School of Public Health), Cleaveland Floyd, Harry Lilienthal, E. A. Locke, H. Allan Novak and F. M. Rackemann of Boston, Massachusetts; Dr. Nahum Pillsbury, South Braintree, Massachusetts; Dr. W. I. Clark, Worcester, Massachusetts; Drs. Robert A. Cooke, M. Fishberg, Edgar Mayer, James Alex. Miller of New York, New York; Dr. Harry Bray of Ray Brook, New York; Drs. E. R. Baldwin, Lawrason Brown and L. U. Gardner of Saranac Lake, New York; Dr. John J. Lloyd of Rochester, New York; Dr. Fred H. Heise of Trudeau, New York; Dr. Jeremiah Metzger of Tyrone, New Mexico; Drs. C. Hartwell Cocke and Paul Ringer of Asheville, North Carolina; Dr. Paul McCain of Sanatorium, North Carolina; Dr. H. R. M. Landis of Philadelphia, Pennsylvania; Dr. H. L. Barnes of Wallum Lake, Rhode Island; Dr. C. D. Parfitt, Gravenhurst, Ontario; Dr. Jabez H. Elliott of Toronto, Ontario; Dr. D. A. Stewart of Ninette, Manitoba.

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FURTHER STUDIES ON THE PATHOLOGICAL SIGNIFICANCE OF THE LEUCOCYTIC REACTION IN TUBERCULOSIS

1. A Presentation of a Leucocytic Index with a Calculator to Facilitate Its Computation[1]

A. M. CRAWFORD

It is generally recognized that the leucocytic reaction is of significance in a variety of pathological conditions. The degree of abnormality is revealed by the variations in the number of the five cell types. These cell types present a complex and constantly varying picture which is exceedingly difficult to evaluate properly. When an attempt is made by clinicians to interpret the leucocytic picture in terms of the underlying pathological involvement, many difficulties are encountered and much confusion arises. It was felt that a leucocytic index which would be sensitive to and vary with the variations of the component cell types would simplify the interpretation of the leucocytic reaction.

In his article on the pathogenesis of tuberculosis (1) Medlar has stated that three leucocytic types participate in the tuberculous lesions at different stages of the pathological process. The neutrophiles predominate in the phase of abscess-formation, of cavitation and of ulceration. The lymphocytes are the chief cells in the healing of the tuberculous lesion. The monocytes participate predominantly in the formation of monocytic tubercles and in the early reparative process following caseation.

In a subsequent article (2) Medlar has suggested an interpretation of the pathological processes of the tuberculous lesions through the circulating leucocytes, since the tuberculous lesions are in large part composed of leucocytes which must of necessity pass through the circulating blood before arriving at their destination. He states that "the establishment of the clinical diagnosis of tuberculosis is necessary before the leucocytes can be of aid in the interpretation of the status of the tuberculous process." In this article he arbitrarily established three types of leucocytic formulae, the septic, the hyperplastic and the nonseptic, stating that

[1] From the Hegeman Memorial Laboratory of the Sanatorium of the Metropolitan Life Insurance Company, Mt. McGregor, New York.

"these are fairly characteristic and are indicative of three phases of the disease process." For more complete interpretation of these leucocytic formulae the reader is referred to the original article.

Medlar's conception of the pathology of tuberculosis, to this observer, seems to be a logical explanation of the various phases of the tissue reaction. From the above review of Medlar's evaluation of the leucocytic reaction, it is apparent that four constantly varying components of the picture have to be considered before interpretation as to the type of underlying tuberculous process can be determined, and before a conclusion as to how the patient is handling his tuberculosis may be arrived at. The significance of these four variables has been pointed out by Medlar; namely,

1. The neutrophile plays the chief rôle in tuberculous abscess-formation and in the extension of tuberculous ulcers.
2. The lymphocyte predominates when a tuberculous lesion is healing.
3. The mononuclear leucocyte is the chief cell of new tubercle-formation.
4. The total leucocyte counts by themselves roughly indicate the volume of deranged tissue with which the leucocytes have to cope.

An evaluation of these four components enables one to determine the status of the tuberculous process and to decide whether the leucocytic picture indicates a nonseptic or healing process, a hyperplastic process with formation of new tubercles which are not undergoing abscess-formation, or a septic picture, with or without new tubercle-formation and with abscess-formation or extension of tuberculous ulcers.

The definitely unfavorable or septic type of pathological process is indicated when neutrophiles are above 65 per cent and lymphocytes are below 25 per cent. If, to this unfavorable picture, the picture of new tubercle-formation as indicated by an increase in monocytes be added, the process becomes more unfavorable.

New tubercle-formation as indicated by an increase in monocytes in the absence of abscess-formation is more favorable.

When healing is taking place, as indicated by approximation of the percentage of neutrophiles and the percentage of lymphocytes with little or no evidence of new tubercle-formation, as evidenced by a monocytic percentage below 10, the pathological process is most favorable.

In the interpretation of the leucocytic picture in terms of the underlying tuberculous process as outlined by Medlar, we are primarily concerned with the relation of the percentage of neutrophiles to the percentage of lymphocytes. (The total of these cell types gives the same relationship.)

This ratio may be expressed N%:L% or $\frac{N\%}{L\%}$. It is apparent that an $\frac{N\%}{L\%}$ ratio of $\frac{1}{1}$ or less represents healing. As this ratio increases, it represents a less favorable status of the tuberculous process. When the $\frac{N\%}{L\%}$ reaches $\frac{60\%}{30\%}$ or $\frac{2}{1}$, an unfavorable type of pathological process, a lesion in which the trend toward abscess-formation is overbalancing the tendency to heal, is indicated, and further increases in the ratio indicate an increasingly unfavorable type of pathological process. From this, we see that an $\frac{N\%}{L\%}$ ratio of $\frac{1}{1}$ or less is ideal, $\frac{2}{1}$ represents beginning unfavorable, and further increases of, say, $\frac{3}{1}$ or $\frac{4}{1}$ represent more unfavorable pathological processes.

Thus, we have a progression of ratios which Medlar has evaluated in terms of the status of the tuberculous lesion. These ratios themselves might be used as an index of the variations of these two components. However, the most convenient progression of values for such an index was obtained through the use of these formulae:

1: When $\frac{N\%}{L\%}$ ratio is between $\frac{1}{1}$ and $\frac{2}{1}$ (favorable range of ratios)

$$\frac{(N\% - 1)}{(L\%\quad)}20$$

This gives a mathematical progression of values for any mathematical progression of ratios between $\frac{1}{1}$ and $\frac{2}{1}$: *e.g.*

Ratio Progression,	$\frac{1}{1}$	$\frac{1.1}{1}$	$\frac{1.2}{1}$	$\frac{1.3}{1}$	$\frac{1.4}{1}$	$\frac{1.5}{1}$	$\frac{1.6}{1}$	$\frac{1.7}{1}$	$\frac{1.8}{1}$	$\frac{1.9}{1}$	$\frac{2}{1}$
Ratio Value Progression	0	2	4	6	8	10	12	14	16	18	20

2: When $\frac{N\%}{L\%}$ ratios are above $\frac{2}{1}$ (unfavorable range of ratios)

$$\frac{(N\%)}{(L\%)}\ 10$$

This gives a mathematical progression of values for any mathematical progression of ratios above $\frac{2}{1}$: *e.g.*

Ratio Progression	$\frac{2}{1}$	$\frac{2.1}{1}$	$\frac{2.2}{1}$	$\frac{2.3}{1}$	$\frac{2.4}{1}$	$\frac{2.5}{1}$	$\frac{2.6}{1}$	$\frac{2.7}{1}$	$\frac{2.8}{1}$	$\frac{2.9}{1}$	$\frac{3}{1}$
Ratio Value Progression	20	21	22	23	24	25	26	27	28	29	30

It will be apparent that ratio value 0 represents the ideal or best $\frac{N\%}{L\%}$ ratio, which in turn represents the best type of tuberculous process; that the ratio value progression between 0 and 20 represents an increasing $\frac{N\%}{L\%}$ ratio of from $\frac{1}{1}$ to $\frac{2}{1}$, which indicates a less favorable type of tuberculous process; and that the ratio value progression above 20 represents $\frac{N\%}{L\%}$ ratios above $\frac{2}{1}$ which indicates increasingly unfavorable tuberculous processes.

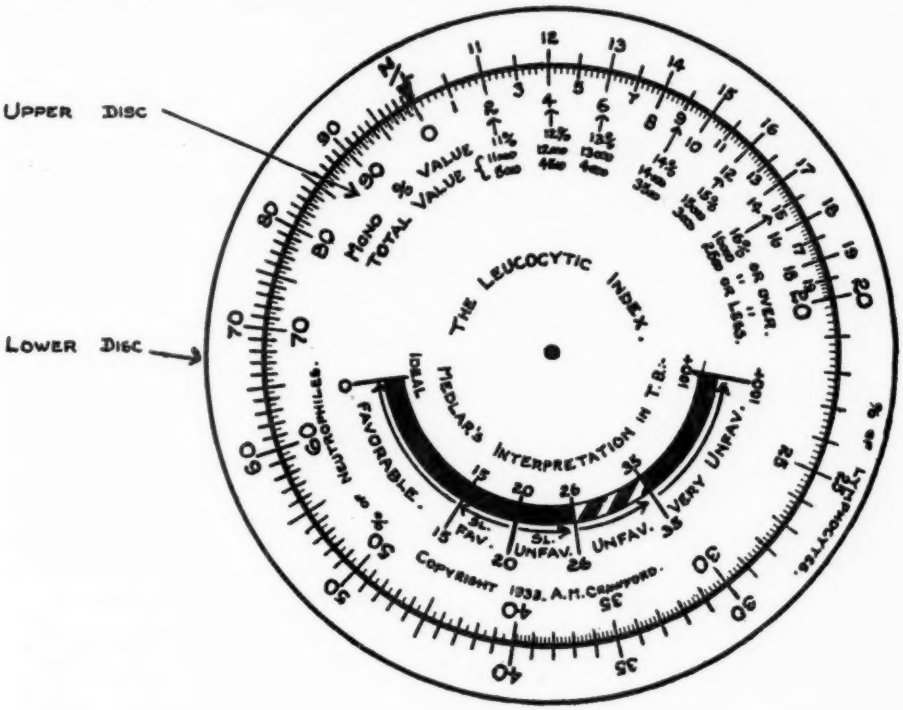
For convenience in calculation, I have devised a simplified circular slide-rule which gives quickly and accurately the ratios for all the possible ranges of the percentage of neutrophiles and the percentage of lymphocytes. For the various actual ratios, I have calculated the ratio values in accordance with the formulae given, and applied these values directly on the face of the calculator instead of the actual ratios. By means of this calculator, the $\frac{N\%}{L\%}$ ratio value for any $\frac{N\%}{L\%}$ ratio is readily obtained.

An illustration of the calculator is shown and calculators may be secured from the author.[2]

The two other abnormal components of the leucocytic picture, namely, an abnormal percentage of monocytes and an abnormal total, have been given values in terms of the selected $\frac{N\%}{L\%}$ ratio values. The values assigned to abnormal monocyte percentage or abnormal total were determined by deciding arbitrarily in consultation with Dr. Medlar how significant were these possible abnormalities of themselves in terms of the $\frac{N\%}{L\%}$ ratio value. It will be noted that since elevation of monocytes indicates new tubercle-formation, and an abnormal total cell count indicates unfavorable pathological activity, as described above, these components of the blood picture, when present, indicate a less favorable type of tuberculous process. Their effect of themselves on the picture as a whole

[2] Address: 7356 Twelfth Street, Detroit, Michigan.

tends to shift the picture toward the unfavorable side. In the presence of a healing lesion, the effect of either one of these factors tends only to make the picture less favorable. In the presence of a healing lesion, the



CALCULATOR FOR DETERMINING THE LEUCOCYTIC INDEX.

DESCRIPTION OF CALCULATOR

The *Calculator* is a modified rotary slide-rule, and consists of two concentric discs, an upper and a lower. The upper disc has on its margin a geometrical and arithmetical progression of the percentage of neutrophiles usually encountered. It also shows the table of values for any abnormal percentage of monocytes and for any abnormal total cell count. It also has a scale which shows the interpretation of any index in terms of favorable or unfavorable pathological activity when evaluated according to Medlar's conception. The lower disc has a geometrical and arithmetical progression of the percentages of lymphocytes usually encountered.

To determine the *Leucocytic Index*, place the percentage of neutrophiles opposite the percentage of lymphocytes. Read off the N/L ratio value under N/L. Add to this the value for an abnormal percentage of monocytes or for an abnormal total cell count, if present. The result is the *Leucocytic Index*.

Medlar's interpretation of any index obtained may be noted by reference to the scale provided on the face of the *Calculator*.

effect of these two factors together may make the picture definitely unfavorable. In the presence of an elevated $\frac{N\%}{L\%}$ ratio, and an elevated mono %, and an abnormal total, the picture as a whole is more unfavorable. It was felt that in Medlar's conception, in the presence of an ideal $\frac{N\%}{L\%}$ ratio, i.e. $\frac{1}{1}$, the most abnormal mono % or the worst total should, of itself, be equivalent to an $\frac{N\%}{L\%}$ ratio of $\frac{1.75}{1}$. So the range of these abnormalities from normal to the worst possible, have been given values in terms of the equivalent $\frac{N\%}{L\%}$ ratio values of from 0 to 15, in accordance with the accompanying table:

TABLE 1

Equivalent values of abnormal monocytic percentages and of abnormal total cell counts in terms of $\frac{N\%}{L\%}$ *ratio value (formula 1)*

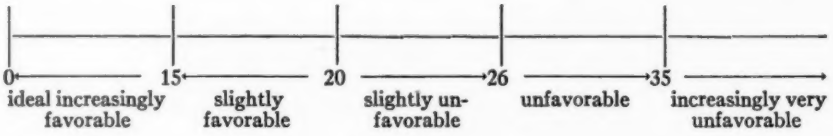
ABNORMAL MONOCYTIC PERCENTAGE	LEUCOCYTOSIS	LEUCOPOENIA	EQUIVALENT $\frac{N\%}{L\%}$ RATIO	EQUIVALENT $\frac{N\%}{L\%}$ VALUE
11	11,000	5,000	$\frac{1.1}{1}$	2
12	12,000	4,500	$\frac{1.2}{1}$	4
13	13,000	4,000	$\frac{1.3}{1}$	6
14	14,000	3,500	$\frac{1.45}{1}$	9
15	15,000	3,000	$\frac{1.6}{1}$	12
16+	16,000+	2,500−	$\frac{1.75}{1}$	15

The assigned values of these two when added to the $\frac{N\%}{L\%}$ ratio value give a final value to the total amount of pathological activity indicated by any given leucocytic picture. This final value we call the *Leucocytic Index* which is derived for any given leucocyte picture by the following formula:—

The Leucocytic Index equals the value of $\frac{N\%}{L\%}$ *ratio as obtained by formulae 1 and 2, plus the value of elevation of monocytes as obtained from table 1, plus the value of abnormal total cell count as obtained from table 1.*

INTERPRETATION

Since the *Index* varies as the abnormal components of the leucocytic formula vary, it is capable of interpretation. The interpretation on the basis of Medlar's conception of the type of pathological activity in the tuberculous lesion as indicated by the leucocytic formula is as follows:



In using the *Leucocytic Index*, Dr. Medlar urges that one should always remember that it is merely an index or indicator which is sensitive to and varies with the significant components of the leucocytic formula. Its variation, which is easily determined through the use of the *Calculator*, merely shows in a simple and mechanical way the variation of the significant components of the *Leucocytic Formula*. It is only a conventional shorthand symbol intended to represent these variations. In order to find out what abnormal factors are involved and hence the actual state of the underlying pathological activity, one must analyze in the light of Medlar's conception, the index obtained from any given leucocytic picture.

The following examples show how the *Index*, while giving the sum of all the unfavorable components of the blood picture, may be used to determine the type of tuberculous process indicated by the blood picture:

Example 1:

Neutrophiles 60%—$\frac{60}{30}$–$\frac{2}{1}$—by Formula 1 $\left(\frac{60-1}{30}\right)$ 20..... 20

Lymphocytes

Monocytes 8% (From table 1)..... 0

Total 8,000 (From table 1)..... 0

Leucocytic Index..... 20

Index 20 is interpreted as beginning slightly unfavorable pathological activity. (See interpretation.) The type of tuberculous process represented is found by reference to the count given and it is noted that the activity is represented entirely by the $\frac{N\%}{L\%}$ ratio, which indicates that the pathological activity is entirely made up of the tendency toward abscess-formation rather than toward healing.

Example 2:

Neutrophiles	55%	$-\frac{55}{27.5}-\frac{2}{1}$— by formula 1 $\left(\frac{55}{27.5}-1\right)20$....	20
Lymphocytes	27.5%		
Monocytes	15%	(From table 1).....	12
Total	8,000	(From table 1).....	0
Leucocytic Index		.....	32

Index 32 is interpreted as unfavorable,—approaching very unfavorable. (See interpretation.) The pathological activity indicated here is found to be composed of the same $\frac{N\%}{L\%}$ ratio as in example 1, with the added unfavorable factor of greatly increased monocytes which indicates new tubercle formation. This added unfavorable factor accounts for the more unfavorable interpretation.

Example 3:

Neutrophiles	55%	$-\frac{55}{27.5}-\frac{2}{1}$— by formula 1.....	20
Lymphocytes	27.5%		
Monocytes	15%	(From table 1).....	12
Total	15,000	(From table 1).....	12
Leucocytic Index		.....	44

Index 44 is interpreted as very unfavorable (See interpretation.) The status of the pathological process is identical with that of example 2 excepting that the unfavorable factor of a leucocytosis has been added, rendering the whole picture more unfavorable.

CHARTING

Chart 1 is included to show how a serial record of the interpretation of an individual case may be kept in the case history. This chart is as

easily followed as that of the temperature or pulse. At *1*, pneumothorax was instituted; at *2*, pneumolysis was done. The clinician may at a glance determine the pathological progress of the tuberculous lesion.

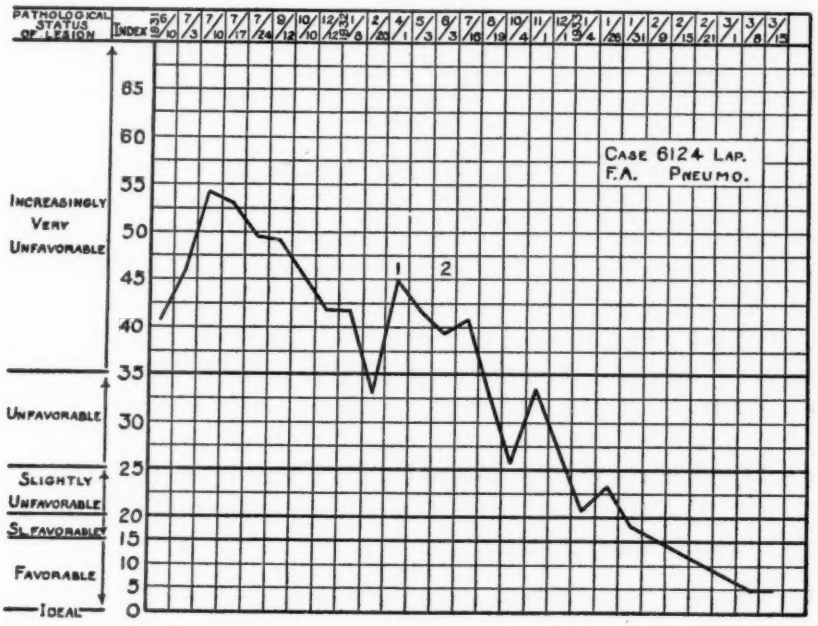


CHART 1

SUMMARY

1. Medlar's conception of the evaluation of the leucocytic reaction in the blood as found in cases of tuberculosis has been reviewed.

2. A *Calculator* has been devised for quickly and accurately determining the $\frac{N\%}{L\%}$ ratio value and for supplying the equivalent values for an abnormal elevation of monocytes and for abnormal total cell counts. This calculator is shown in the foregoing article.

3. From these values the *Leucocytic Index* is readily obtained for any given leucocytic picture.

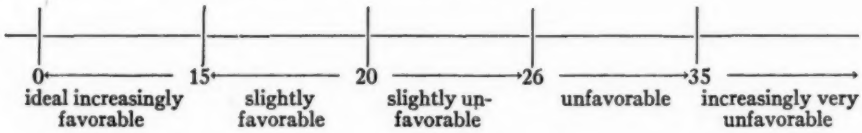
The *Leucocytic Index* is obtained by adding:

a: The $\frac{N\%}{L\%}$ ratio value.

b: The value of abnormal monocyte percentages.

c: The value of abnormal total cell counts.

4. Interpretation of the *Index* is given in terms of a favorable or unfavorable type of pathological activity as follows:



The *Leucocytic Index* is suggested as a short cut to correct interpretation of the Leucocytic reaction in terms of favorable or unfavorable pathological activity as evaluated by Medlar. It is only a conventional short-hand symbol intended to represent the variation of the significant components of the leucocytic picture. The degree of pathological activity having been determined by the *Index*, it is urged that the components of leucocytic formula be studied in order to get a complete understanding of the phase of the tuberculous process with which we are dealing. Medlar's conception of the significance of the rôle of each of the cell-types in the pathogenesis of the disease may thus be readily and accurately applied and his conception of the pathological status of the tuberculous process determined.

I am indebted to Dr. Medlar for his kindly cöoperation and beg to acknowledge especially his suggestions in working out the table of equivalent values; and I am also indebted to Dr. W. H. Ordway and to the clinical staff for many helpful suggestions.

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FURTHER STUDIES ON THE PATHOLOGICAL SIGNIFICANCE OF THE LEUCOCYTIC REACTION IN TUBERCULOSIS

2. A Presentation of the Pathological Concept through the Use of the Leucocytic Index in Selected Groups of Tuberculous Cases[1]

E. M. MEDLAR

In the preceding article (pp. 611–620), Crawford has presented a calculator with which a leucocytic index may be obtained. In this way, a single number, a summary so to speak, is obtained which indicates how far from zero, the ideal leucocytic index in tuberculosis, a single leucocytic count varies. Crawford emphasized the fact, which I also wish to stress, that the leucocytic count should be examined to determine which factors are responsible for the index number. This method of summarizing leucocytic counts I heartily endorse. I believe such a method will aid clinicians to obtain a more uniform interpretation of leucocytic counts in tuberculosis.

By the use of index numbers a comparison of groups of tuberculous cases is possible. Such a comparison was not possible, in a simple way, with the method of interpretation which I advocated in a previous article (1). I utilize, therefore, this opportunity to use Crawford's method to present again the pathological concept which I have presented before.

This concept was based upon extensive studies on the pathogenesis of tuberculosis (2) (3). It was found that, in the healing phase of the lesion, the lymphocyte became more and more the predominant cell as the healing process progressed. It was also found that in the progressive-spreading lesions which led to death, the neutrophile predominated. In between these two extremes, the monocyte played a very important rôle. With the innocuous, healing lesion at one extreme and the dangerous spreading lesion at the other, it was felt that a logical explanation could be given to the lesions which lay between.

This interpretation was then transferred to the circulating leucocytes which, it was believed, would reflect the status of the tuberculous pathological process. Arguments in favor of this thesis were presented in a

[1] From the Hegeman Memorial Laboratory of the Sanatorium of the Metropolitan Life Insurance Company, Mt. McGregor, New York.

previous communication, to which the reader is referred (1). Since that publication, data have been accumulating until at the present time about 400 tuberculous cases have been investigated with over 20,000 leucocytic counts available. These additional data give added weight to the original concept.

The purpose of this communication is to compare in tabular form groups of tuberculous cases, and to present in this way the pathological process from that which tends to heal to a very serious condition too often terminating in death even in our present advanced stage of phthisiology. Table 1 shows the distribution of the leucocytic indices from zero to 100, that is, from what I originally termed the typical nonseptic through the hyperplastic to the very septic count. The purpose of the table is to give the idea that as the index numbers proceed from zero toward 100, the more unfavorable does the picture become. It must be clearly understood that the grouping of the index numbers into many subdivisions is made to indicate a progression of events rather than with any idea of dogmatism. The interpretation of the significance of these subdivisions is based wholly upon the author's judgment gained from a rather extensive study of the problem. In this interpretation all of the index numbers within a division are considered as of equal value.

In the compilation of the data in table 1, given in the analysis below, the following method was used. An equal number of consecutive leucocytic counts were taken from each case. The index numbers for these counts were then obtained and these indices were sorted out into the different divisions. All of the indices falling within the same division were then added together. Thus, in column 1, 255 leucocytic indices are given of which 94 were within the range 0–5, 134 were between 6 and 15 and the remaining 27 ranged between 16 and 21.

The author's interpretation of the pathological significance of these various groupings of indices is as follows:—

0–5—Very favorable. 16–21—Slightly favorable.
6–15—Favorable. 22–26—Slightly unfavorable.
27–35—Unfavorable.
36+—Very unfavorable.

In using Crawford's calculator both plus and minus factors may be obtained in the neutrophile–lymphocyte ratio. The author is unable to evaluate the real significance of the minus factors in tuberculous cases.

At present all minus factors are interpreted as if they were at 0— that is as an ideal leucocytic index for a tuberculous case. On the plus-side factors rising to over 900 may be obtained with occasional leucocytic counts. From actual experience it has been found that the number of leucocytic counts in tuberculous cases in which the sum of the factors will give an index over 100 are infrequent. Consequently all leucocytic indices over 100 are arbitrarily considered at a value of 100.

It will be noted that all index numbers above 35 are interpreted as very unfavorable. It is recognized that a leucocytic index of 80 represents a more severe pathological condition in tuberculosis than an index of 40 or 50. But all such counts are very unfavorable. From his experience the author has not been able to determine just how much significance should be placed on the rather large fluctuations that commonly occur in the leucocytic indices in tuberculous cases with very unfavorable pathological outlook. Consequently, it has seemed best to group all leucocytic indices above 35 as very unfavorable and to recognize that there may be different degrees of unfavorableness, which at present do not seem capable of definite evaluation.

The different groups of individuals represented in columns 1 to 5 in table 1 are here designated.

Column 1 represents a group of 17 cases of moderately and far-advanced tuberculosis with 15 consecutive weekly counts on each. From the pathological angle leucocytic indices, such as these, may be regarded as evidence of a favorable handling of the pathological process during this period.

Column 2 shows the distribution of the index numbers in a group of 17 normal individuals (4) in New York City on each of whom 13 consecutive weekly counts were done. The very least that should be looked for in a group of tuberculous cases would be for them to present a similar distribution of leucocytic indices.

Column 3 is the record of 50 cases of ambulatory moderately and far-advanced tuberculosis now in the sanatorium. There were 15 consecutive weekly counts on each case. Judged from the pathological angle, this group is composed of cases which range from favorable to very unfavorable. It will be noted that the leucocytic indices extend into groups of index numbers beyond those in column 2. In other words they are worse than normal.

Column 4 presents 25 cases of moderately and far-advanced tuberculosis with 15 consecutive weekly counts. These are all bed cases. There

is a marked shift to the higher index numbers. Pathological interpretation is very unfavorable.

Column 5 gives the leucocytic picture within six months of death in 15 cases who have died from tuberculosis in the institution. Each case is represented by ten consecutive counts. Note that there are no leucocytic indices in the first four brackets.

The data as to the groups of cases and the distribution of leucocytic indices contained in table 1 were submitted to the Statistical Bureau of the Metropolitan Life Insurance Company for analysis as to its significance. The following is the report submitted and edited by Dr. A. J. Lotka:

Statistical Analysis of Leucocytic Count Data on Four Groups of Tuberculous Patients, Compared with a Normal Nontuberculous Group as a Control

There was submitted for statistical analysis the subjoined table 1 showing the distribution of 1,754 leucocytic count records (expressed as *Index Numbers*) made on 124 persons classified as follows:

1. A group of 17 tuberculous cases judged as favorable from a pathological viewpoint.
2. A group of 17 nontuberculous persons serving as a "normal control."
3. A group of 50 ambulatory tuberculous cases, judged from a clinical standpoint as doing well.
4. A group of 25 bed cases judged to be doing poorly with their tuberculosis.
5. A group of 15 persons who had died of tuberculosis at the sanatorium.

The analysis is here concerned only with the distribution of the leucocytic counts resulting from the above classification, which was accepted as fundamental datum. The merits of the classification itself or of the leucocytic count index are not under discussion in this statistical analysis.

A mere ocular inspection of table 1 immediately reveals a systematic downward shift in the grouping of the material as we pass from column 1 to column 5. While this is plainly visible to the eye without any refined analysis, it is desirable to obtain a numerical measure of the feature thus exhibited.

An obvious expedient is to observe the mean of each distribution in columns 1 to 5 respectively. This mean has been indicated in the table at the bottom of each column. As was to be expected, we find a clear

sequence of numbers as follows: 8.6, 14.6, 21.0, 49.2, 58.8, for the means corresponding to columns 1, 2, 3, 4 and 5, respectively. The mean for

TABLE 1

Analysis of Dr. Medlar's leucocytic count data on tuberculous patients at Mount McGregor

LEUCOCYTIC COUNT INDEX	NUMBER OF COUNTS WITH SPECIFIED INDEX				
	No. 1 (17 persons)	No. 2 Control (17 persons)	No. 3 (50 persons)	No. 4 (25 persons)	No. 5 (15 persons)
Total	255	224	750	375	150
0– 5	94	34	72	—	—
6–15	134	91	184	3	—
16–21	27	49	143	13	—
22–26	—	35	140	19	—
27–35	—	15	138	64	15
36–45	—	—	48	93	26
46–55	—	—	19	64	32
56–65	—	—	4	42	31
66–75	—	—	1	20	13
76–85	—	—	1	37	17
86–95	—	—	—	20	9
96–100	—	—	—	—	7
Mean index	8.6	14.6	21.0	49.2	58.8
Dispersion about mean index, σ.	4.9	7.9	11.9	19.5	18.9

TABLE 2

Differences in mean index and in dispersions about mean index, taken between groups

GROUPS DIFFERENCED	DIFFERENCE IN MEAN INDEX	DIFFERENCE IN DISPERSION ABOUT MEAN INDEX
Nos. 1–2	−6.0± .6	−3.0± .4
Nos. 3–2	6.4± .7	4.0± .5
Nos. 4–2	34.6±1.1	11.6± .8
Nos. 5–2	44.2±1.6	11.0±1.2
Nos. 3–1	12.4± .5	7.0± .4
Nos. 4–1	40.6±1.1	14.6± .7
Nos. 5–1	50.2±1.6	14.0±1.1
Nos. 4–3	28.2±1.1	7.6± .8
Nos. 5–3	37.8±1.6	7.0±1.1
Nos. 5–4	9.6±1.8	−.6±1.3*

Note: Excepting the case marked thus (*), all the differences are statistically significant.

the control column is 14.6, intermediate between that of columns 1 and 3. The progression from column 1 to column 5 shows itself very clearly and obviously in the series of means.

To complete the inquiry we must determine whether the differences between these means are statistically significant. These differences are, in point of fact, so marked, that applying a numerical test may almost seem an unnecessary refinement. However, as a matter of statistical routine, and to place the matter beyond any possibility of doubt, the test has been carried out. It consists, according to familiar custom, in determining the standard error of the differences between the means of the two members of any pair to be compared.

Table 2 shows the results of these comparisons. In the first four lines, each of the groups 1, 3, 4 and 5, is compared with the control group 2. Group 1 has a mean lower than that of the control, by six units, with a standard error of .6. The difference here is, then, ten times its standard error, indicating a very high degree of probability that this difference is not due to mere accident, but is due to a difference in the inherent nature of the contrasted material.

Similar indications are shown for the other pairs brought into comparison. In every instance there is a very high degree of significance, on the usual understanding that, when a difference exceeds twice its standard error, significance can be assumed with a high degree of probability.

In addition to the means, there are shown, in the bottom line of table 1, the dispersions about the mean. The dispersion is a measure of the scatter of the observations about the mean value. It will be observed, for instance, that in column 4 the several items spread all the way from a leucocytic index of 6 to one of 95, whereas in the first column the observations spread only from 0 to 21. Thus the counts are much more closely concentrated in the first group than in the fourth group. This difference in concentration shows itself in the dispersion, which is 4.9 for the first column and 19.5 for the fourth column. This tells us that in persons with favorable leucocytic counts, these are more closely concentrated about the mean than in persons with unfavorable counts, in whom they tend to scatter over a considerable range.

These variations in the scatter of the leucocytic counts are also not a matter of accident, as is shown by the analysis of the differences in the dispersions, exhibited in the last column of table 2. In every case except the last, the differences are found to be significant. The one case where the difference is not significant is that which relates to the comparison of column 4 and column 5. Apparently when the leucocytic count becomes distinctly unfavorable the scatter of the leucocytic counts does not further increase appreciably. In the example shown there is an actual

slight and insignificant decrease, to which no particular interest can be attached.

SUMMARY

A re-presentation of the author's concept of the pathological significance of leucocytic counts in tuberculous cases is given, using Crawford's calculator to obtain the leucocytic indices. The concept is presented through the use of selected groups of moderately and far advanced tuberculosis. The distribution of leucocytic indices in normal non-tuberculous persons is used as a control. The author's interpretation of the significance of the index numbers is given. A statistical analysis of the data is presented.

The material presented shows that the pathological concept can be demonstrated by using selected groups of tuberculous cases and that all of these groups vary from the normal "control." The statistical analysis shows that the differences between the groups are statistically significant.

A test of the validity of this concept will be presented in a future communication.

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FURTHER STUDIES ON THE PATHOLOGICAL SIGNIFICANCE OF THE LEUCOCYTIC REACTION IN TUBERCULOSIS

3. A Comparison of the Leucocytic Reactions as Found with and without Artificial-Pneumothorax Therapy[1,2]

E. M. MEDLAR

The interpretation of leucocytic reactions as found in the circulating blood is at best a roundabout way of interpreting the pathological processes present in tissues. From a pathological point of view it is always preferable to have tissue that is the seat of the disease for careful study rather than to have to rely upon a circuitous method of interpretation into which extraneous factors may enter. In tuberculosis, where the pathological lesions lie largely in tissues beyond the scope of direct biopsy, an indirect biopsy through leucocytic interpretations should prove of considerable value, provided such interpretations can be placed upon a reasonable and valid basis.

When an attempt is made to determine the significance and accuracy of leucocytic interpretations in tuberculosis several angles of approach are possible. The approach of preference would be through the use of experimental animals, where the leucocytic interpretation and the condition in the tuberculous lesions could be directly compared by killing the animals at desired stages of development of the disease process. A very serious, though to the author not valid, objection to this method is that animal tuberculosis is not human tuberculosis and, therefore, whatever evidence found could not be transferred. A second method of approach would be to interpret on a pathological basis the change or lack of change in the leucocytic reaction in tuberculous cases under treatment. While such interpretations may be correct from a pathological point of view, they meet with resistance from the clinical point of view because they have not been accepted or proved as valid. A third approach

[1] From the Hegeman Memorial Laboratory of the Sanatorium of the Metropolitan Life Insurance Company, Mt. McGregor, New York.

[2] Presented at a joint session of the Clinical and Pathological Sections at the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 17, 1931.

would be to compare interpretations at discharge and on readmission of patients to a tuberculous institution. Here the group available would be small unless a long time had elapsed. A fourth method would be to make interpretations on a group of cases discharged and, after a time, compare these with the events subsequent to discharge on a basis of work, incapacitation and death. If a group of sufficient size, two years or longer having elapsed since discharge, were available this method would give the most complete data for clinicians relative to the correctness and possible value of leucocytic interpretations based upon the pathogenesis of tuberculosis.

The present paper deals with a comparison of the leucocytic reaction, before treatment with a period six months or longer after treatment is begun, in hospitalized tuberculosis cases receiving pneumothorax therapy and those not receiving such therapy, but under accepted sanatorium regimen.

PNEUMOTHORAX GROUP

In this group have been included all of the cases that have had artificial pneumothorax six months or longer and on which leucocytic records were available before or at the beginning and during treatment. Records were available on cases from 1927. In all there were 109 cases suitable for the study.

The purpose of the study was to determine whether with this method of therapy there had occurred a change in the leucocytic reaction and, if so, to what extent. In all the cases weekly or biweekly leucocytic counts were available. To represent each case the first four consecutive counts were taken as indicative of the type of pathological process present previous to the institution of pneumothorax. The record during treatment was then carefully studied and, at the period in which the greatest improvement in the leucocytic picture was present, four consecutive counts were taken to represent the change following the institution of pneumothorax. The leucocytic indices, using Crawford's *Calculator* (1), were determined, and these were sorted out into the various subdivisions, as shown in whole group, table 1. It will be noted that the average index has been reduced from 40.7 before to 26.5 after the institution of pneumothorax therapy. In other words the pathological process has improved, when the group as a whole is considered.

The whole group was then analyzed, on a pathological basis, to determine the degree of pathological improvement and the number of cases

present in the different groups. The following arbitrary standards for this analysis were set up:

1: Favorable pathology: At least one-half of the counts must have an index less than 22 and no count with index above 26 is allowed.
2: Very unfavorable pathology: At least one-half of the counts must have an index of 35 or higher and no count with an index less than 22 is allowed.

TABLE 1

Distribution of leucocytic indices in pneumothorax cases

LEUCOCYTIC COUNT INDEX	NUMBER OF LEUCOCYTIC COUNTS WITH SPECIFIED INDEX							
	Total (109 cases)		Favorable pathology (33 cases)		Unfavorable pathology (40 cases)		Very unfavorable pathology (36 cases)	
	B	A	B	A	B	A	B	A
Total	436	436	132	132	160	160	144	144
0– 5	1	29	1	29	—	—	—	—
6–15	15	83	8	67	7	16	—	—
16–21	23	61	13	30	10	31	—	—
22–26	31	80	13	6	14	66	4	8
27–35	128	91	47	—	49	39	32	52
36–45	97	43	26	—	36	6	35	37
46–55	64	22	12	—	25	2	27	20
56–65	39	10	8	—	8	—	23	10
66–75	18	12	3	—	7	—	8	12
76–85	13	3	—	—	2	—	11	3
86–95	7	2	1	—	2	—	4	2
96–100	—	—	—	—	—	—	—	—
Average leucocytic index	40.75	26.5	34.4	11.3	38.5	24.2	49.1	43.0
Dispersion about average index	16.76	16.34	14.4	5.9	15.6	7.4	16.7	15.0
Differences in averages (B–A)	14.25 ±1.12		23.1 ±1.4		14.3 ±1.4		6.1 ±1.9	
Differences in dispersion (B–A)	0.42 ±.79		8.5 ±1.0		8.2 ±1.0		1.7 ±1.3	

In the above table the number after the ± sign is the standard error. In any instance a finding equal to or exceeding twice its standard error is regarded as significant.

3: Unfavorable pathology: All cases which do not fit into either group 1 or group 2 are placed in this group.

To illustrate how the cases were sorted the following examples are given:

Case 1: Leucocytic indices are 39, 46, 25 and 36. This case goes into the very unfavorable group.

Case 2: Leucocytic indices are 9, 17, 18 and 23. This case goes into the favorable group.
Case 3: Leucocytic indices are 29, 9, 25 and 21. This case goes into the unfavorable group.

In the analysis, the leucocytic indices, after pneumothorax therapy was instituted, were used for sorting the cases into the different pathological groups. After this sorting was completed the leucocytic indices for each group before pneumothorax was begun were assembled. In table 1 is given the analysis in the favorable, unfavorable and very unfavorable pathological groups. In this table column *B* represents the index grouping before and column *A* six months or longer after the institution of pneumothorax.

Several points of interest are found in this analysis. About one-third of the cases are present in each pathological group,—33 favorable, 40 unfavorable and 36 very unfavorable. It will be seen that the average index in column *A* very unfavorable is about four times as large as in column *A* favorable, whereas in the corresponding columns *B* there is a much smaller difference. In other words these two groups were more nearly alike, pathologically, before pneumothorax than after. In comparing columns *B* and *A* favorable group, it will be seen that the average index has decreased 23.1 units whereas in the very unfavorable group there has been a decrease of but 6.1 units. From a pathological point of view the pneumothorax therapy has effected a very marked improvement in the favorable, a moderate improvement in the unfavorable, and very little improvement in the very unfavorable group.

COMPARISON OF PNEUMOTHORAX AND NONPNEUMOTHORAX CASES

While it is possible to demonstrate the change or lack of change in the type of pathology in pneumothorax as is shown above, such a change may be present to a similar extent in tuberculous cases not receiving such treatment. To determine whether such a thing be true, 265 nonpneumothorax cases on which leucocytic records were available from their admission and which had remained in the sanatorium six months or longer were sorted out on the same basis of pathological interpretation as was used with the pneumothorax group. Favorable, unfavorable and very unfavorable groups were established. The distribution of the cases were as follows: favorable, 103; unfavorable, 90; and very unfavorable, 72.

To have the two groups comparable, the pathological picture, as interpreted from the leucocytic reaction, should be as nearly similar as possible in the two groups on the first leucocytic counts. To obtain such a similarity it was necessary to delete 84 cases in the favorable group, as in these cases the pathological process, according to the leucocytic interpretation, on admission was not as bad as that present in the pneumothorax group. It is interesting that in this deletion 50 per cent of the minimal, 30 per cent of the moderately advanced and 15 per cent of the far advanced cases were removed from the group as a whole.

TABLE 2

Distribution of leucocytic indices in 109 pneumothorax and 179 nonpneumothorax cases

LEUCOCYTIC INDEX NUMBERS	PATHOLOGICAL PROCESS IMPROVED				PATHOLOGICAL PROCESS NOT IMPROVED			
	Pneumothorax		Non-pneumothorax		Pneumothorax		Non-pneumothorax	
	B	A	B	A	B	A	B	A
Total	292	292	252	252	144	144	464	464
0– 5	1	29	—	4	—	—	—	4
6–15	15	83	—	46	—	—	19	15
16–21	23	61	—	72	—	—	30	41
22–26	27	72	21	81	4	8	74	92
27–35	96	39	100	38	32	52	114	175
36–45	62	6	76	10	35	37	90	78
46–55	37	2	29	1	27	20	54	33
56–65	16	—	12	—	23	10	38	15
66–75	10	—	6	—	8	12	18	10
76–85	2	—	5	—	11	3	19	3
86–95	3	—	3	—	4	2	12	2
Average leucocytic index	36.63	18.38	39.56	21.45	49.11	42.96	39.79	32.95
Dispersion about average index	15.19	9.35	13.09	7.95	16.67	15.04	18.43	13.18

To simplify the comparison the favorable and unfavorable groups were combined into a group in which there had occurred an improvement in the pathological process while the very unfavorable group was left as one in which the pathological improvement was insignificant.

In table 2 is listed the leucocytic-index distribution before (*B*) and 6 months or longer after (*A*) the two types of therapy were instituted. It will be noted that in both pneumothorax and nonpneumothorax groups

the same phenomenon of shift or lack of shift in the pathological picture occurs. In the pneumothorax group, however, two-thirds of the cases show a pathological improvement, whereas in the nonpneumothorax group but one-third show a similar change. Another point of interest, not shown in the condensed table, is that in the pneumothorax group about one-third show a marked improvement while in the nonpneumothorax group a similar improvement was present in only one-tenth of the group. In the last two lines of this table is given the average index numbers and the dispersion about this index for each column.

In table 3 is given a comparison of the differences in average leucocytic index and the dispersion about the average index in the improved and

TABLE 3

A comparison of the various groups of pneumothorax and nonpneumothorax cases

COMPARISONS MADE	"B" CASES MINUS "A" CASES				PNEUMO MINUS NONPNEUMO				UNIMPROVED MINUS IMPPOVED CASES			
	Improved		Unimproved		Improved		Unimproved		Pneumo		Nonpneumo	
	Pneumo	Nonpneumo	Pneumo	Nonpneumo	"A" Cases	"B" Cases	"A" Cases	"B" Cases	"A" Cases	"B" Cases	"A" Cases	"B" Cases
Differences in means of average leucocytic index	18.25 ±1.05	18.11 ±0.96	6.15 ±1.87	6.84 ±1.05	−3.07 ±0.74	−2.93 ±1.21	10.01 ±1.39	9.32 ±1.63	24.58 ±1.37	12.48 ±1.65	11.50 ±0.79	0.23 ±1.18
Differences in dispersion about average leucocytic index	5.84 ±0.74	5.14 ±0.68	1.63 ±1.32	5.25 ±0.74	1.40 ±0.52	2.10 ±0.86	1.86 ±0.99	−1.76 ±1.15	5.69 ±0.97	1.48 ±1.17	5.23 ±0.55	5.34 ±0.83

In the above table the figure after the ± sign denotes the standard error. If the figure preceding the ± sign exceeds twice the standard error it is to be considered significant. Thus, in the first column, 18.25 ± 1.05 the standard error is exceeded almost 18 times and hence the difference between the two means is to be considered very significant.

unimproved, the *B* and *A* and the pneumothorax and nonpneumothorax cases. The main point of interest shown in the table is that the improved pneumothorax group had slightly less severe pathological involvement on admission than the improved nonpneumothorax group, whereas the reverse was true in the unimproved groups. The degree of shift in both the pneumothorax and nonpneumothorax cases was practically identical.

In both groups of cases the extent of tuberculosis ranges from minimal to far advanced. Hence a tabulation was made to determine the effect of the methods of treatment in the different stages of the disease. These data are presented in table 4. The findings were of interest. In the pneumothorax group 93.8 per cent of the minimal cases showed improvement, while in the far-advanced only 52 per cent showed a similar

trend. In contrast to this, in the nonpneumothorax group there was no significant difference in the number of cases improved between the minimal (37 per cent) and far-advanced (33 per cent) groups. In every instance the percentage of improved cases in the pneumothorax group was

TABLE 4

The distribution of the pneumothorax and nonpneumothorax cases

EXTENT OF DISEASE	PNEUMOTHORAX			NONPNEUMOTHORAX		
	Total	Improved	Unimproved	Total	Improved	Unimproved
Total	109	73 (67%)	36 (33%)	179	63 (35.2%)	116 (64.8%)
Minimal	16	15 (93.8%)	1 (6.2%)	43	16 (37.2%)	27 (62.8%)
Moderately advanced	62	42 (67.7%)	20 (32.3%)	73	26 (35.6%)	47 (64.4%)
Far advanced	31	16 (51.6%)	15 (48.4%)	63	21 (33.3%)	42 (66.7%)
In Chi square* test, P χ		0.0147			0.9148	

* In the Chi square test the figure 0.0147 means the chances are 1 in 68 that in assembling such data the differences between minimal, moderately and far advanced cases given above in the pneumothorax group might have occurred by accident. Evidence is therefore pretty strong that the excess of improvement in the minimal and moderately advanced cases as compared with the far advanced is not an accident but is inherent in the nature of the case. On the other hand the figure 0.9148 in the nonpneumothorax means that the chances are 91 in 100 that such differences as noted are due simply to chance. In this test unity is certainty. The nearer the approach toward unity the more certain it becomes that any differences noted are due to chance.

TABLE 5

A tabulation of the deaths in the pneumothorax and nonpneumothorax cases

EXTENT OF DISEASE	DEATHS IN PNEUMOTHORAX CASES			DEATHS IN NONPNEUMOTHORAX CASES		
	Total	Improved	Unimproved	Total	Improved	Unimproved
Total	7 (6.4%)	—	7 (19.4%)	24 (13.4%)	1 (1.6%)	23 (19.8%)
Minimal	—	—	—	—	—	—
Moderately advanced	2 (3.2%)	—	2 (10.0%)	11 (15.1%)	1 (3.8%)	10 (21.3%)
Far advanced	5 (16.1%)	—	5 (33.3%)	13 (20.6)%	—	13 (30.9%)

The percentages given in the above table represents the percentage of the corresponding group shown in table 4.

higher than the corresponding nonpneumothorax group. The data also suggest that it is easier to control a small than a large amount of disease in the pneumothorax group.

A tabulation of deaths from tuberculosis, given in table 5, shows that

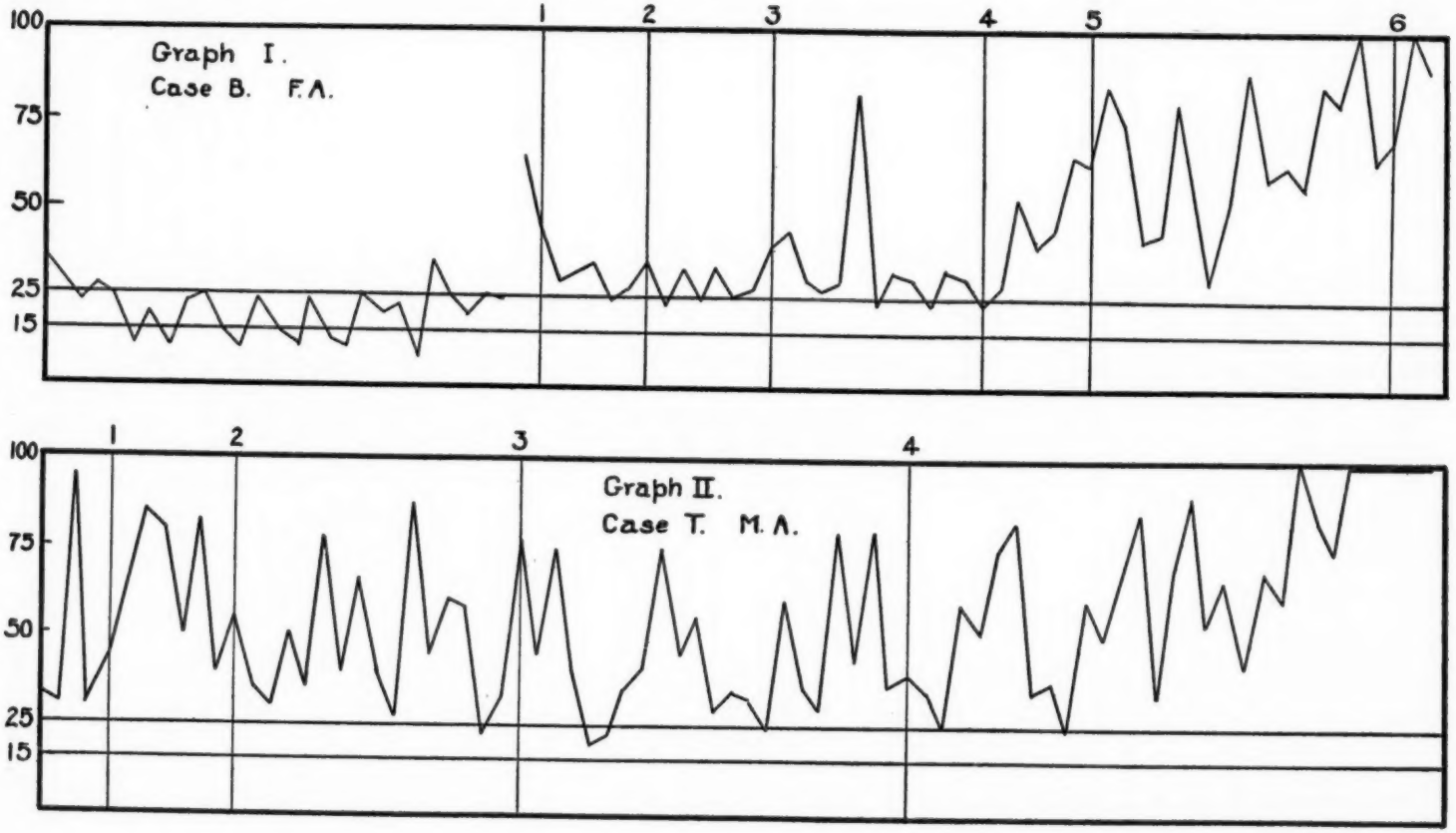
in both the pneumothorax and the nonpneumothorax groups the death-rate is much the larger in the pathologically unimproved cases and that in each group the highest death-rate is in the far-advanced cases.

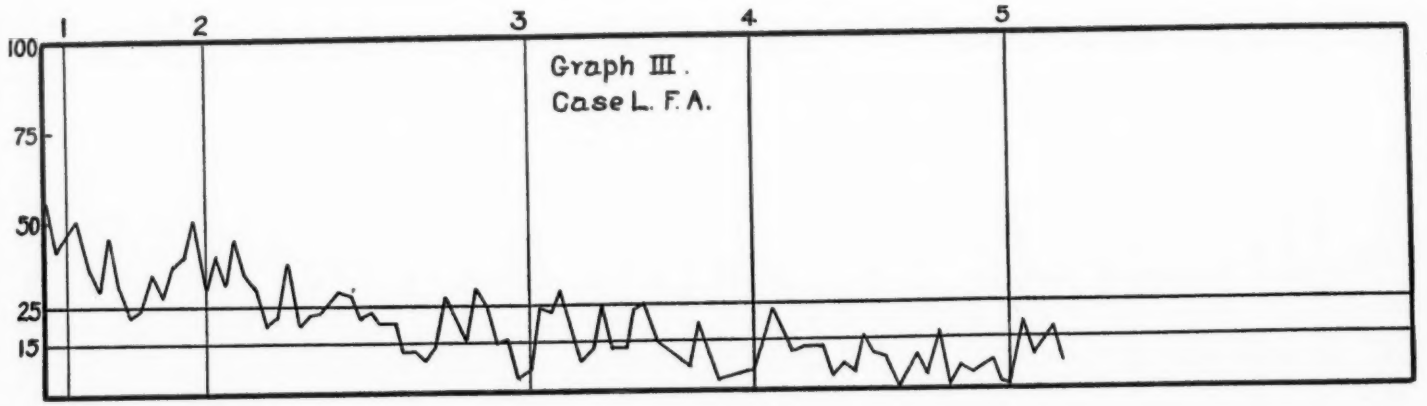
The above data deal entirely with the study of groups of tuberculosis cases. Such studies are necessary in order that broad general principles may be elucidated. While it is essential that such principles be clearly portrayed the chief concern of the clinician is whether the interpretation of groups as a whole can be applied to the individual case. In the application of therapeutic measures it is the individual rather than the group in whom the chief concern lies.

To illustrate the way in which the pathological interpretation given above may be applied to the individual case 4 pneumothorax cases have been selected. Graphs 1 and 2 represent two cases in which pneumothorax therapy failed to control the pathological process and death ensued. Graphs 3 and 4 are two cases which have shown very marked clinical improvement, and they show that the pneumothorax therapy has effectively controlled the pathological process. In the graphs the points of prime importance are indicated by vertical lines. The horizontal line drawn at 15 indicates that all counts below this line are pathologically favorable. Between the lines 15 and 25 the counts range between slightly favorable to slightly unfavorable. Above 25 all counts are unfavorable and as they approach 100 the more unfavorable they become. For plotting purposes all leucocytic counts with an index above 100 are graphed as if they were at 100. Such counts are seldom present except in the very last stages of tuberculosis. In these graphs the general trend of the pathological process rather than the significance of any single count is the important point.

Graph 1: Case B. Admission 5/17/30. Female; age 21; F.A., R. 2, L. 2, cavity. Favorable clinical progress. Discharged apparently arrested 1/17/31. The graph before the break in the line shows the pathological picture during residence. On the whole it is more on the unfavorable than the favorable side.

Case readmitted 6/15/31. Symptoms reappeared while at work and X-ray showed an increase on readmission over plates of previous residence. Pneumothorax instituted 7/14/31 (1). Collapse ineffective because of adhesions. Pneumolysis performed 8/15/31 (2). Very good collapse followed, but cavity did not close. X-ray increase in opposite lung 4/7/32 (3). Collapsed lung allowed to reëxpand 11/7/32 (4). X-ray increase in reëxpanded lung 2/1/33 (5). Further increase in contralateral lung 6/13/33 (6). Death 8/26/33. During this residence the sputum was positive for tubercle bacilli on 14 out of 16 examinations.


Graph I.
Case B. F.A.
100
75
50
25
15
1
2
3
4
5
6
Graph II.
Case T. M.A.
100
75
50
25
15
1
2
3
4


1
2
3
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100
75
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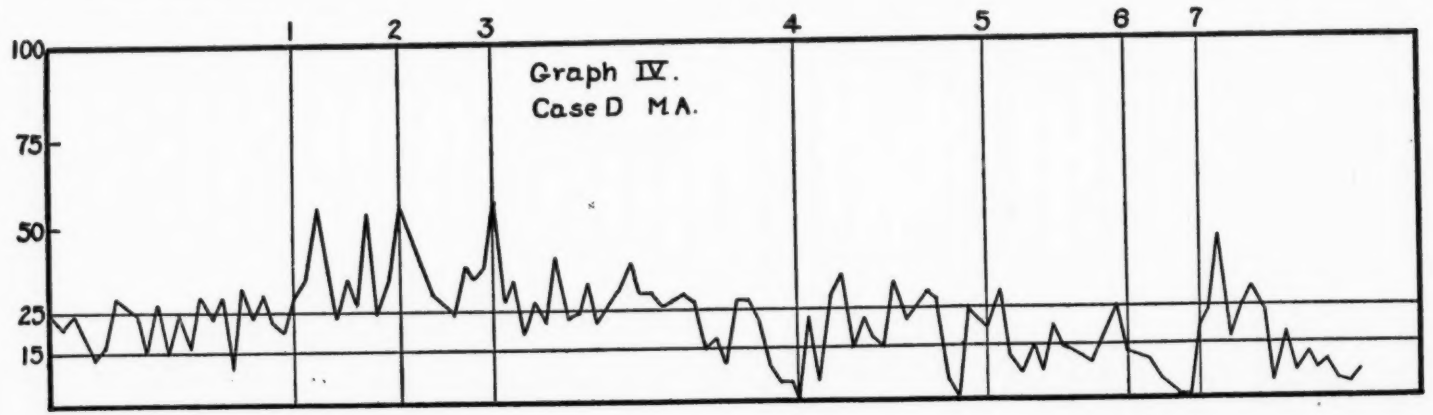
25
15
Graph III.
Case L. F. A.


1
2
3
4
5
6
7
100
75
50
25
15
Graph IV.
Case D M A.

The leucocytic graph shows that the pathological process was much worse on readmission than on discharge. Pneumothorax and pneumolysis brought about a slight improvement of the pathological process but never brought it into the favorable range. As the pathological process became worse the graph shows a more unfavorable trend.

Graph 2: Case T: Female; age 24. Diagnosis M.A., (R), R.2, L.1. Admitted 11/21/28. Clinical symptoms were very slight during first part of residence. Patient was increased to 30 minutes' exercise with no untoward results up to March, 1929, when the X-ray showed an increase of the disease. At this point exercise was discontinued and bed-rest therapy was resumed. Further increases by X-ray were noted 7/1/29 and 11/7/30. Pneumothorax instituted 11/10/30 (1). Because of adhesions pneumothorax was only partially effective and pneumolysis was performed 5/29/31 (2). Following this there was satisfactory collapse. Tuberculous empyema developed 9/15/31 (3). A marked spread occurred in the opposite lung on 10/14/33 (4). Death occurred on 3/26/34. There was no expectoration up to 8/1/33. Fourteen sputum examinations up to this date were all negative. Following this 8 more sputum examinations were made and they were all positive for tubercle bacilli.

The leucocytic graph shows that the pathological trend was distinctly unfavorable throughout. Only a few counts were done prior to pneumothorax but they were all unfavorable. As the disease-process spread and the volume of pathological involvement increased, the graph shows a distinctly more unfavorable trend.

Graph 3: Case L.: Male; age 37. Diagnosis F.A. (R. & P.), R.3, L.1. Admitted 2/27/32. Pneumothorax instituted 3/17/32 (1). Because of adhesions collapse was only partial and pneumolysis was done 6/24/32 (2). Following pneumolysis satisfactory collapse was obtained and the patient made very good clinical progress. Exercise was begun 3/7/33 (3) and has been continued to the present time with no untoward results. On two occasions (4 & 5) the patient has been allowed to return to his home for a week's visit. Up to 5/1/32 the sputum contained tubercle bacilli. Since that date the sputum has gradually decreased to no expectoration and all samples examined have been negative for tubercle bacilli. The patient is still under treatment.

The leucocytic graph shows that the pathological process has slowly changed from unfavorable to favorable and that this condition has been fairly well maintained. It will be noted that the two excursions home caused a mild upset of the pathological process toward the unfavorable side. This condition has promptly changed to favorable on return to sanatorium regimen.

Graph 4: Case D: Female; age 19. Diagnosis M.A. (R.) R.1 (?) L.2. Admitted 5/1/30. Patient seemed to be making satisfactory progress up to

8/18/30 (1), when X-ray showed an increase. A further spread of the disease was noted by X-ray on 11/14/30 (2). Pneumothorax was advised but refused. A further increase was noted by X-ray on 3/10/31 (3) and pneumothorax therapy was instituted. During this period the clinical condition of the patient became serious. Favorable collapse was obtained in spite of the presence of adhesions. Following the institution of pneumothorax the patient made excellent clinical progress and exercise was begun on 2/15/32 (4). This was continued until 3/9/33 (5) when X-ray showed a small spread in the opposite lung. Pneumolysis was performed on 7/2/33 (6). In October, 1933, (7) because of the very satisfactory collapse and excellent clinical condition the patient was allowed full bathroom privileges. The patient is still under treatment. The sputum was positive on two examinations only and there has been no expectoration since October, 1933.

The leucocytic graph shows an unstable pathological process from the beginning. This became distinctly worse with the increase of the disease process. Following pneumothorax the pathological process changed gradually to favorable and then reverted to unfavorable with the advent of exercise. On being returned to bed rest the process again returned to favorable with a distinct improvement following pneumolysis. With the granting of bathroom privileges the process again reverted to unfavorable and has since gradually returned to favorable. Such an unstable pathological process demands very careful watching if it is to be successfully controlled. The only evidence of this instability aside from the leucocytic graph since the institution of pneumothorax was a spread in the contralateral lung about one year after exercise was begun.

DISCUSSION

The interpretation of the data presented above is based on the pathogenesis of tuberculosis. This article is concerned in no way with the clinical interpretation as to whether the collapse was effective or as to whether there has occurred a satisfactory clinical improvement. A comparison of the clinical judgment with the pathological interpretation was not undertaken because the majority of cases under consideration in the pneumothorax group were still under treatment. Again, a considerable lapse of time must occur following completion of such therapy before sound judgment can be rendered and cases available for such a comparison were too few in number to warrant any comparison. With a sufficient amount of proper data such a comparison should prove of interest.

The author is aware of the fact that the evidence given and its interpretation is based very largely on a logical concept, not generally accepted as established fact, of what the leucocytic reaction ought to be when judged on the basis of the pathogenesis of the disease tuberculosis.

At best it is a roundabout way to interpret the pathology in tissue inaccessible to direct biopsy. It is however as direct as any interpretations attempted upon the circulating blood. In any event, all such interpretations, whether in nephritis, diabetes, pneumonia or appendicitis, are logical deductions based upon the underlying pathological state. During life the best that can be obtained is presumptive proof; absolute proof can be obtained only with death. As presumptive proof the change or lack of change in the leucocytic reaction, the differences between the pneumothorax and nonpneumothorax groups and the leucocytic-index graph in selected cases are offered. As absolute proof the evidence, as shown in tuberculous deaths, is given.

In previous articles (2) (3) the author has stressed the fact that the leucocytic reaction can only give a running story of the disease process under consideration. A single leucocytic count can tell only what is the pathological status of the moment. Serial counts can suggest the trend. Sufficient observation can establish the stability or instability of the pathological process on the favorable or unfavorable side. From such studies valuable information may be gained and a logical impression may be formulated.

The data herein given are offered with the suggestion that they be used in the interpreting of the status of the pathological process in a collapsed tissue in which the use of the X-ray and physical examinations are largely of no avail. It would seem that it is the nearest approach to the pathological process during life. It is not infallible but the evidence given suggests that, with due care, the deductions arrived at can be of considerable value.

In the interpretation of the running-story in any given case it is the trend rather than the individual count that is of greatest importance. A single count may be favorable or unfavorable, but if the majority of counts are at variance with the single one then the major trend should be relied upon in the interpretation. The goal to be striven for is to get the leucocytic reaction into the favorable range and to keep it there. No effort should be spared to attain this end.

If the leucocytic interpretation of the above data may be considered reliable then it should be possible to judge the effectiveness of collapse therapy, not by the amount of pulmonary collapse but rather by the effect of the collapse upon the leucocytic picture. It may be possible that in one case a moderate collapse, even with adhesions present, may be pathologically effective whereas in another individual nothing short

of complete collapse will obtain the desired results. There would appear to be numerous problems in collapse therapy wherein careful leucocytic studies may give very valuable information.

There is one point in the data submitted which should have very serious consideration. It is quite apparent that the less the amount of disease the more effectively can it be handled by collapse therapy. With this point in mind the author suggests that if a tuberculous case shows a persistently unfavorable leucocytic reaction under bed-rest regimen surgical intervention should be seriously considered. And such intervention should not be too long delayed as the tuberculous abscesses present are liable to rupture and the disease unnecessarily spread.

There are many problems which it is necessary for those responsible for the care of tuberculous cases to solve. The data given in this article are submitted with the hope that they may afford a clearer insight into the disease that must be controlled if the patient and not the disease is to conquer.

CONCLUSION

A pathological analysis by use of leucocytic interpretations of 109 pneumothorax cases is given.

A comparison of 109 pneumothorax and 179 nonpneumothorax cases on a pathological basis is presented.

The data suggest that pneumothorax therapy controls the pathological process in a higher percentage of cases than does the usual sanatorium regimen. The data also suggest that with this type of treatment it is easier to control a small than a large volume of tuberculosis.

The author is indebted to Dr. A. J. Lotka, Assistant Statistician of the Metropolitan Life Insurance Company for the statistical analysis given in the tables. The author desires to express his appreciation for many helpful criticisms to Dr. W. H. Ordway, Physician in Charge, and others of the clinical staff of the sanatorium of the Metropolitan Life Insurance Company. He is also indebted to the clinical staff for permission to include the abstracts of the individual tuberculous cases.

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FURTHER STUDIES ON THE PATHOLOGICAL SIGNIFICANCE OF THE LEUCOCYTIC REACTION IN TUBERCULOSIS

4. A Test of the Validity of the Pathological Interpretation Placed upon the Leucocytic Reaction[1]

E. M. MEDLAR

In previous communications on leucocytic studies in tuberculous cases the following papers have been presented: *A leucocytic index* (*1*); the *pathological concept* (*2*); and a *pathological analysis of tuberculous cases with and without artificial-pneumothorax therapy* (*3*). The present paper will deal with a pathological analysis of a group of tuberculous cases selected by Drs. Ordway and Pesquera of the clinical staff. In this selection the clinical history, serial roentgenograms, physical findings and sputum examination were used as the criteria for selection, the first two being given the most weight. All cases included in the group were judged by the clinicians to be active cases of pulmonary tuberculosis which had been discharged from the institution prior to 1933.

The analysis given below will be based upon the pathogenesis of the disease tuberculosis as presented by the author in previous communications (4) (5) (6). In brief, the two extremes of the pathological process may be stated as follows: The dangerous tuberculous lesions are tuberculous abscesses in which the neutrophile is the predominant cellular element. The healing tuberculous lesion is one in which the lymphocyte becomes more and more the predominant cell. Between these two extremes the monocyte plays an important rôle.

The only method of approach to the type of cellular pathology in pulmonary tuberculosis during life is through the circulating leucocytes. When this method is used one has to assume the privilege of placing the circulating leucocytes into the pathological lesions. Before such a procedure is permissible the leucocytic picture of normal persons must be thoroughly understood. With the establishment of what may be considered as the normal variation of the leucocytic picture in normal healthy

[1] From the Hegeman Memorial Laboratory of the Sanatorium of the Metropolitan Life Insurance Company, Mt. Gregor, New York.

persons the problem which confronts one in tuberculous cases is how the leucocytic picture is to be interpreted, for such persons are no longer in a state of normal health. In other words it is essential to interpret the leucocytic picture in the tuberculous on the basis of the pathology of their disease rather than with reference to what a healthy, nontuberculous individual should show. Leucocytic counts in tuberculous cases may be abnormal for normal persons but for the tuberculous the counts may be very favorable or very unfavorable, depending upon how they fit into the pathological process. Again, leucocytic counts which may be considered within normal for healthy persons may be either favorable or unfavorable for tuberculous cases, depending upon which end of normality the counts lie.

TABLE I

Distribution of leucocytic indices in normal and in tuberculous cases

LEUCOCYTIC INDEX NUMBER	30 HEALTHY NONTUBERCULOUS PERSONS	45 M.A. & F.A. TUBERCULOUS CASES, DEAD OF TUBERCULOSIS	45 M.A. & F.A. TUBERCULOUS CASES. JUDGED PATHOLOGICAL CHANGES FAVORABLE ON DISCHARGE
Total	478	1,895	2,035
0–10	156 (32%)	20 (1%)	705 (35%)
11–20	194 (41%)	88 (4%)	674 (33%)
21–30	113 (24%)	256 (13%)	439 (22%)
31–40	15 (3%)	396 (22%)	127 (6%)
41–50	—	304 (17%)	47 (2%)
51–60	—	259 (13%)	22 (1%)
61–70	—	174 (9%)	10 (.5%)
71–80	—	135 (7%)	7 (.3%)
81–90	—	94 (5%)	2 (.1%)
91–100	—	55 (3%)	2 (.1%)
100 plus	—	114 (6%)	—
Average leucocytic index	15.06	50.94	16.99

In an attempt to clarify this conception of the leucocytic picture, the author presents in table I the distribution of leucocytic indices as obtained with the *Calculator* devised by Crawford (1) for the following:

Column 1 represents 487 leucocytic counts on 30 carefully selected normal persons. The distribution of leucocytic indices shows that 73 per cent of the counts have an index of 20 or less and that in but 3 per cent were the index numbers above 30. In other words leucocytic indices above 30 are rarely found in normal persons and it is quite likely that

such counts are distinctly abnormal although found in a so-called state of health.

Column 2 represents the leucocytic counts on 45 M.A. and F.A. cases that have died of tuberculosis. In all there were 1,895 counts. The number of counts per individual varied from 6 to over 100. All of the leucocytic counts obtained during residence in the sanatorium were included. In no instance was the leucocytic record of less than three months' duration, and in the majority of cases the period of observation was from one to three years. Twenty of the cases died in from one to four years after discharge and the remainder died in the institution. The data presented were obtained at this institution between the years 1927 and 1933. The distribution of the leucocytic indices in this column is in marked contrast to the one for normal persons. It shows 83 per cent of the leucocytic counts with an index of over 30 and only 4 per cent with and index of 20 or less. Since this represents a considerable volume of data on a group of tuberculous cases on whom the end-result is known, it seems fair to assume that leucocytic counts with indices above 30 indicate distinctly unfavorable pathological involvement in tuberculous cases.

Having established the unfavorable pathological picture in column 2 it is now necessary to establish the opposite, or favorable, pathological picture. The only way this can be established from a pathological point of view is to take those cases which, on discharge from the institution, had a leucocytic picture consistent with a healing tuberculous lesion. For this purpose 45 M.A. and F.A. tuberculous cases were selected. They represent the same period of time as column 2. In all, 2,035 leucocytic counts were available. The number of counts per individual varied from 10 to over 100. In the majority of cases the leucocytic record extended back to admission to the sanatorium. The distribution of the leucocytic indices is shown in column 3 which is practically the reverse of column 2. Since these individuals have been discharged for from 1 1/2 to 6 years it is of interest to know their status as of 1934. In this group there have been no deaths. Forty have remained at work without any clinical evidence of relapse. Five have returned to the sanatorium for further treatment of their pulmonary tuberculosis.

Of the 5 cases that were readmitted to the sanatorium, three returned with favorable leucocytic counts and two showed leucocytic reactions of an unfavorable type. During the second hospitalization the leucocytic reaction changed to a favorable type in the 2 cases which had an un-

favorable type on readmission and they have been discharged, having shown marked clinical improvement. None have died or have been critically ill since readmission.

From column 3 one may judge that leucocytic counts having an index of less than 20 are distinctly favorable in tuberculous cases, since 68 per cent of the 2,035 counts come within this range. This is further substantiated by the fact that, of the last six counts on each individual before discharge, there were none with indices above 30 and only about 25 per cent with indices between 21 and 30. Practically all of the leucocytic counts having indices above 30 occurred during the first portion of the sanatorium residence.

We have then established, with sufficiently large groups of cases and a large enough volume of leucocytic counts, the two extremes of the leucocytic reaction in tuberculosis. Having these data it would seem possible to analyze any group of tuberculous cases on a pathological basis.

PATHOLOGICAL ANALYSIS OF 281 TUBERCULOUS CASES

Using the data presented in table I it is possible to limit in a purely arbitrary manner the requirements for three pathological groups. The criteria for these groups are established solely for the purpose of analyzing a group of 281 clinically selected cases of active pulmonary tuberculosis on a pathological basis.

The standards which the author has used for the analysis are as follows: In all minimal cases the last four and in all moderately and far advanced the last six consecutive leucocytic counts available represent each case. The smaller number of counts were used in the minimal cases because of their shorter stay in the institution.

1: Favorable pathological group: No leucocytic counts with an index above 26 are allowed. In moderately and far advanced cases at least one-half of the counts must have indices below 22. Minimal cases having all counts with indices of 26 or less are included without any other requirements.
2: Very unfavorable pathological group: In all cases at least one-half of the counts must have indices of 35 or over and no counts with indices below 22 are allowed.
3: Unfavorable pathological group: This group includes all cases which do not fit the requirements of either of the other groups.

Future work may show that these pathological groups are too arbitrary or *vice versa*. However, some standard must be accepted in order that

the reasonableness of the pathological interpretation may be tested by what has happened to date to the group studied.

Table II shows the distribution on a basis of pathology of the 281 cases when the above criteria were used.

TABLE II

Distribution of 281 tuberculous cases at Mt. McGregor according to extent of disease and pathological group

PATHOLOGICAL GROUP	EXTENT OF DISEASE			
	All cases	Minimal	Moderately advanced	Far advanced
	Number			
Total	281	63	130	88
Favorable	74	31	29	14
Unfavorable	126	24	62	40
Very unfavorable	81	8	39	34
	PERCENTAGE OF ALL EXTENTS OF DISEASE			
Total	100.0	22.4	46.3	31.3
Favorable	100.0	41.9	39.2	18.9
Unfavorable	100.0	19.1	49.2	31.7
Very unfavorable	100.0	9.9	48.1	42.0
	PERCENTAGE OF ALL PATHOLOGICAL GROUPS			
Total	100.0	100.0	100.0	100.0
Favorable	26.3	49.2	22.3	15.9
Unfavorable	44.9	38.1	47.7	45.5
Very unfavorable	28.8	12.7	30.0	38.6

From table II it will be seen that, of the whole group, 26 per cent were pathologically favorable and 29 per cent very unfavorable on discharge. The minimal cases show the largest percentage (49 per cent) of pathologically favorable and the smallest percentage (13 per cent) of very unfavorable, while the far-advanced group had the smallest percentage (16 per cent) of favorable and the largest percentage (39 per cent) of very unfavorable cases. On the basis of the amount of pathological involvement this result would naturally be assumed. It is of interest that the analysis coincides with the assumption.

It is of equal interest to see how the leucocytic indices are distributed in the various groups. The indices for ease of compilation were assembled

into various subdivisions, interpreted as follows: 0–5, very favorable; 6–15, favorable; 16–21, slightly favorable; 22–26, slightly unfavorable; 27–35, unfavorable; 36–45, 46–55, etc., all very unfavorable. In this grouping all leucocytic indices below zero or on the minus side were arbitrarily given a value of zero and all with indices over 100 were given a value of 100. Such counts, although they occur, were found to be relatively infrequent. All leucocytic indices within the subdivisions are considered of equal value.

The distribution of the leucocytic indices for the 281 cases shown in table II is given in table III. At the bottom of the table is given the average leucocytic index and the dispersion about the average index for each respective column.

Table III shows that in the group as a whole 482 counts (31 per cent) have indices below 22 and 788 (50 per cent) have indices above 26. When the group is split up into a minimal, moderately advanced, and far-advanced classification, this distribution of leucocytic indices assumes greater significance. The percentages of indices below 22 are as follows: Minimal, 49 per cent; M.A., 30 per cent; F.A., 23 per cent. For indices above 26 the following percentages are found: Minimal, 31 per cent; M.A., 49 per cent; and F.A., 62 per cent. This shows that the leucocytic counts in the whole favorable range are most numerous in the minimal and least in the far-advanced cases, whereas the reverse is true in the unfavorable range. From this one may judge that the greater the volume and the more severe the pathological changes the more does the leucocytic picture tend to swing into an unfavorable range.

The average leucocytic index for the different stages of disease also illustrate the point discussed above. Thus, in the minimal group the average index is 22.80, in the moderately advanced 28.37, and in the far-advanced 35.93.

The data presented in tables II and III demonstrate that it is possible to subdivide the groups made according to the extent of pulmonary disease into groups of different pathological severity. If it can be shown that the favorable pathological group has many fewer casualties than the very unfavorable one, then the subdivision of the clinical classification of extent of disease into groups according to the severity of the pathological process should prove of great value. This would allow of a definite estimation of the type of pathological activity in an individual tuberculous case.

TABLE III

Distribution of 1,562 leucocytic indices from the 281 tuberculous cases shown in table I according to extent of disease and to pathological grouping

LEUCOCYTIC INDICES	ALL CASES				MINIMAL				MODERATELY ADVANCED				FAR ADVANCED			
	Total	F.	U.F.	V.U.F.	Total	F.	U.F.	V.U.F.	Total	F.	U.F.	V.U.F.	Total	F.	U.F.	V.U.F.
Total	1,562	388	704	470	260	130	98	32	780	174	372	234	522	84	234	204
0–5	69	62	7	—	27	24	3	—	28	26	2	—	14	12	2	—
6–15	213	159	54	—	61	51	10	—	101	68	33	—	51	40	11	—
16–21	200	87	113	—	40	24	16	—	107	40	67	—	53	23	30	—
22–26	292	80	202	10	52	31	20	1	159	40	114	5	81	9	68	4
27–35	342	—	232	110	42	—	35	7	179	—	113	66	121	—	84	37
36–45	237	—	73	164	21	—	12	9	137	—	33	104	79	—	28	51
46–55	88	—	13	75	8	—	—	8	41	—	6	35	39	—	7	32
56–65	36	—	7	29	4	—	1	3	9	—	3	6	23	—	3	20
66–75	30	—	1	29	1	—	—	1	7	—	—	7	22	—	1	21
76–85	32	—	1	31	2	—	—	2	10	—	1	9	20	—	—	20
86–95	14	—	—	14	1	—	—	1	2	—	—	2	11	—	—	11
96–100	9	—	1	8	1	—	1	—	—	—	—	—	8	—	—	8
Average leucocytic index	29.97	13.88	26.99	47.71	22.80	13.81	26.73	47.28	28.37	14.32	26.16	42.34	35.93	13.07	28.43	53.94
Dispersion about average leucocytic index	17.69	7.03	10.02	17.54	15.32	7.40	12.24	15.85	14.41	7.10	9.44	12.76	21.08	6.20	9.69	20.25

TEST OF VALIDITY OF THE PATHOLOGICAL ANALYSIS

The above pathological analysis was made without any reference to the condition of the persons included in the study. The purpose of the study was to determine whether it was possible by using leucocytic counts to establish different pathological groups for the cases as a whole and also for the groups of cases falling within the usual clinical classification of minimal, moderately and far advanced disease. The author believes that the data presented in table II demonstrate the feasibility of establishing pathological groups even when the disease is considered as far advanced. Is it possible to establish the validity of this pathological interpretation?

To determine the soundness and reasonableness of the pathological interpretation the status of each case as of March, 1934, was obtained from the record room, the large part of the information being obtainable because of an excellent follow-up system. All of the cases included in the study had been discharged from the institution for over a year and many of them were discharged five years previous to the present study.

The criteria accepted at the present time for determining the condition of tuberculous cases are death, incapacitation and ability to work. From a pathological point of view death is the criterion of choice, since it is the end of the story from both the clinical and the pathological standpoints. However, in the group of cases analyzed above, this accounted for but 16 per cent of the whole group. The remaining 84 per cent will necessarily have to be judged on the basis of incapacitation or of ability to work. These two criteria are both open to serious objections from a pathological point of view. To attempt to judge the seriousness of any pathological process by a person's ability to work necessarily introduces several factors which may very largely obscure the actual status of the pathological process. The advice of the physician resulting from his appraisal of the clinical condition, the economic status and the psychological reaction of the individual toward his disease are three factors which militate strongly against an unbiased estimation of the actual status of the tuberculous process. Some criteria for a gross estimation of the condition of the tuberculous must however be accepted. The author accepts, with definite reservations, the criteria of incapacitation and of ability to work as the best test available on the tuberculous cases who have not succumbed to the disease. Incapacitation includes cases on whom the report was clinical relapse or inability to work.

Under the heading of working are included those actually at work and those judged as being capable of, but unable to obtain work. Those cases merely reported as living and those on whom there were no data were included under the heading no report.

In table IV is shown the distribution of the tuberculous cases on a basis of work, incapacitated, dead and no report in the whole groups, in the different stages of the disease and according to pathological judgment. A study of the table reveals many points of interest.

The group as a whole shows 56 per cent at work, 26 per cent incapacitated, 16 per cent dead and 2 per cent with no report. When sorted into pathological groups the results on a basis of "at work" show the following

TABLE IV

PATHOLOGICAL GROUPS	ALL CASES				MINIMAL				MODERATELY ADVANCED				FAR ADVANCED			
	Work	Incapacitated	Dead	No report	Work	Incapacitated	Dead	No report	Work	Incapacitated	Dead	No report	Work	Incapacitated	Dead	No report
Total	158	74*	44†	5	50	9*	1†	3	76	39	14	1	32	26	29	1
Favorable	64	7	1†	2	29	—	1†	1	25	4	—	—	10	3	—	1
Unfavorable	69	45	9	3	16	6	—	2	36	21	4	1	17	18	5	—
Very unfavorable	25	22*	34	—	5	3*	—	—	15	14	10	—	5	5	24	—

* 1 case diagnosed pleurisy with effusion, nontuberculous. Case developed moderately advanced tuberculosis within three months.

† 1 minimal case died of coronary disease,—hence a nontuberculous death.

percentages: favorable, 86 per cent; unfavorable, 55 per cent; and very unfavorable, 31 per cent. On a basis of "incapacitation" the percentages are: favorable, 9 per cent; unfavorable, 36 per cent; and very unfavorable, 27 per cent. On a basis of death the percentages show: favorable, 1.4 per cent (nontuberculous death); unfavorable, 7 per cent; and very unfavorable, 42 per cent. When it is considered that the pathological groups were established prior to knowledge of the present status of these cases it would seem that the reasonableness of the pathological grouping was substantiated, even with the crudeness of the criteria available for judging the pathological status in the living cases.

Among those who had died of tuberculosis it was found that 23 were discharged dead from the institution and 21 had died subsequent to

discharge. These latter deaths occurred from 6 months to 5 years after leaving the institution.

Further substantiation of the pathological grouping is shown on a basis of casualties (incapacitation or death). In the group of minimal cases, the favorable pathological group had 3 per cent (a nontuberculous death) and the very unfavorable group 37 per cent casualties. In the group of far-advanced cases, the favorable pathological group had 21 per cent and the very unfavorable 85 per cent casualties. This shows that the less the extent of the disease and the more favorable the leucocytic reaction, the fewer the casualties; also that the greater the extent of disease and the more unfavorable the leucocytic reaction the greater the casualties.

Another point clearly demonstrated in the data is that favorable leucocytic reactions are not absolute proof that clinical and pathological relapses will not occur. Of five cases discharged with a pathologically favorable leucocytic picture who returned to the sanatorium and presented clinical relapses, two showed a definitely worse pathological picture and three did not.

A COMPARISON OF ADMISSION AND DISCHARGE PATHOLOGICAL INTERPRETATION

If, as it appears, unfavorable leucocytic counts represent unfavorable pathological involvement, then the leucocytic reaction should become favorable if the pathological process becomes sufficiently improved. The reverse should also be true. With such a theorem another angle of approach is available to test the validity of the pathological interpretation. The pathological interpretation on admission can be compared with that on discharge. In cases showing definite pathological improvement one should expect to find a smaller percentage of casualties (incapacitation or death) than in those cases which have shown no pathological improvement. To place the pathological interpretation to such a test, all of the cases in the group of 281 who had remained in the sanatorium over 6 months and on whom a sufficiently large number of counts were available were analyzed as above. The admission pathological status of each case was determined by the first 4 consecutive counts and the discharge status by the last four. In all, 187 cases were available for this study. In table V is assembled this group of cases in a comparison of the admission and discharge status relative to the pathological group.

The data in table V show that of the whole group 56 per cent were discharged with the same pathological status as on admission, 37 per cent were improved, and 7 per cent were worse. On discharge the group favorable on admission showed 77 per cent favorable, 19 per cent unfavorable and 4 per cent very unfavorable. A similar comparison in the same order of the unfavorable group gave 28, 62 and 10 per cent; and of the very unfavorable, 17, 38 and 45 per cent. In other words there had occurred a considerable shift in the pathological picture during residence with the major shift being toward an improvement of the pathological process. This is further emphasized by the composition of the pathological groups on discharge. Thus, in the group favorable on discharge 36.4 per cent were pathologically favorable, 36.4 per cent unfavorable and 27.2 per cent very unfavorable on admission. In the group of very

TABLE V

Analysis of 187 cases on a basis of admission and discharge pathological status

PATHOLOGICAL STATUS ON DISCHARGE	PATHOLOGICAL STATUS ON ADMISSION															
	All cases				Minimal				Moderately advanced				Far advanced			
	Total	F.	U.F.	V.U.F.	Total	F.	U.F.	V.U.F.	Total	F.	U.F.	V.U.F.	Total	F.	U.F.	V.U.F.
Total	187	26	71	90	48	14	21	13	90	11	34	45	49	1	16	32
Favorable	55	20	20	15	26	12	9	5	21	7	6	8	8	1	5	2
Unfavorable	83	5	44	34	17	2	11	4	42	3	24	15	24	—	9	15
Very unfavorable	49	1	7	41	5	—	1	4	27	1	4	22	17	—	2	15

unfavorable on discharge 2 per cent were favorable, 14 per cent unfavorable and 84 per cent very unfavorable on admission. In other words 64 per cent of the group favorable on discharge were either unfavorable or very unfavorable on admission while in the group very unfavorable on discharge 84 per cent were in the group very unfavorable on admission. This change in the pathological status of the cases analyzed above can best be appreciated by the change in the leucocytic picture. The following percentages give the salient points of this shift. On admission 748 leucocytic counts were distributed, according to leucocytic indices, as follows: 0–21, 19 per cent; 22–30, 27 per cent; and 31 or over, 54 per cent. On discharge the same number of counts showed the following distribution: 0–21, 34 per cent; 22–30, 30 per cent; and 31 or over 36 per cent. In other words, leucocytic counts within the favorable range

increased 15 per cent, whereas there was a drop of 18 per cent in the distinctly unfavorable range.

If this change in the leucocytic picture means anything then one should expect to find that those cases which have remained in or have entered the favorable group on discharge would show the fewest, and those that have remained in or entered the very unfavorable group would show the greatest number of casualties. To determine the truth of such expectations, table VI has been compiled to show the status as of 1934, one to 5 years after discharge, of the cases shown in table V.

From table VI it is seen that of the 187 persons 64 per cent are at work, 23 per cent incapacitated and 13 per cent dead. For the different pathological groups on discharge the following percentages are shown: Favorable: work, 95 per cent, incapacitated 5 per cent. Unfavorable: work, 57 per cent, incapacitated, 32 per cent; dead, 11 per cent. Very unfavorable: work, 41 per cent, incapacitated 27 per cent; dead, 32 per cent.

The most important thing to determine from the data in the table is whether the status of those, when taken as a group, who changed their pathological status differed from those who did not. Such a comparison is given in table VII.

From table VII it is readily seen that the best group was the one in which the pathological process remained favorable, and that the second best group was the one in which the pathological process at discharge was distinctly improved over that on admission. From this analysis it appears that the leucocytic reaction does indicate the trend of the pathology. An improving leucocytic reaction indicates an improving pathological process, and *vice versa*.

DISCUSSION

The purpose of this paper has been to submit data which would affirm or deny the validity of interpreting the pathological status of tuberculous cases through the circulating leucocytes. These data have been analyzed relative to some of their salient points and it appears to the author that the validity of the pathological interpretation has been substantiated.

An objection relative to the soundness of the pathological interpretation may be raised when it is noted that in the group interpreted as pathologically very unfavorable there are 31 per cent working (table IV). Such an objection must rest upon the assumption that any individual with a serious pathological process would be unable to work. This

assumption is of course contrary to common knowledge in many diseases other than tuberculosis. A chronic nephritic, a chronic cardiac, or a case of malignant tumor may succeed in working for years, and yet no

TABLE VI

Distribution of cases shown in table V on a basis of "at work," incapacitated or dead, 1 to 5 years after discharge from the sanatorium

PATHOLOGICAL GROUPS ON DISCHARGE	ALL CASES ON ADMISSION											
	All cases			Favorable			Unfavorable			Very unfavorable		
	Work	Incapacitated	Dead	Work	Incapacitated	Dead	Work	Incapacitated	Dead	Work	Incapacitated	Dead
Total	119	43	25	23	3	—	43	21	7	53	19	18
Favorable	52	3	—	19	1	—	18	2	—	15	—	—
Unfavorable	47	27	9	3	2	—	23	16	5	21	9	4
Very unfavorable	20	13	16	1	—	—	2	3	2	17	10	14
Minimal												
Total	43	5	—	13	1	—	19	2	—	11	2	—
Favorable	26	—	—	12	—	—	9	—	—	5	—	—
Unfavorable	13	4	—	1	1	—	9	2	—	3	1	—
Very unfavorable	4	1	—	—	—	—	1	—	—	3	1	—
Moderately Advanced												
Total	55	24	11	9	2	—	18	11	5	28	11	6
Favorable	19	2	—	6	1	—	5	1	—	8	—	—
Unfavorable	24	14	4	2	1	—	13	8	3	9	5	1
Very unfavorable	12	8	7	1	—	—	—	2	2	11	6	5
Far Advanced												
Total	21	14	14	1	—	—	6	8	2	14	6	12
Favorable	7	1	—	1	—	—	4	1	—	2	—	—
Unfavorable	10	9	5	—	—	—	1	6	2	9	3	3
Very unfavorable	4	4	9	—	—	—	1	1	—	3	3	9

one would deny that a serious pathological condition existed. May it not be a little hazardous to condemn a pathological interpretation on a basis of 31 per cent "at work," when the other 69 per cent in the same

group are incapacitated or dead? There are too many factors, irrelevant to the pathological process, which determine whether a person works or not, to permit the placing of a great deal of importance on such a criterion. The same may be said relative to incapacitation although there is less objection to such a criterion than to one of working.

There is one thing which seems fairly certain. The leucocytic reaction does indicate the pathological trend. This is of real value, for it enables the physician to definitely estimate whether the pathological process is improving or becoming worse. This evaluation can be obtained on individual patients by making serial leucocytic counts.

Another thing which the pathological interpretation makes possible is an evaluation of the pathological status irrespective of the extent of the disease. The data presented above show this clearly. In the group of minimal cases eight out of 63 were interpreted as pathologically very

TABLE VII

Status as of March, 1934, of 187 tuberculosis cases, according to change in pathological process while at Mount McGregor

	IMPROVED PATHOLOGICAL CHANGE	STATIONARY PATHOLOGICAL PROCESS			RETROGRESSED PATHOLOGICAL CHANGE
		F.	U.F.	V.U.F.	
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
At work	78	95	52	41	46
Incapacitated	16	5	36	24	38
Dead	6	—	12	35	16

unfavorable on discharge and of these 3 have since become moderately advanced cases. In the far-advanced group 14 cases out of 88 were considered as pathologically favorable on discharge and of these none have died, one has had a clinical relapse, 2 are unable to work and 10 have remained at work. To be able to pathologically select cases in this way and to have this selection stand up as well as it does puts in the hand of the clinician a very useful tool.

In previous communications (7) the author has emphasized the fact that the leucocytic reaction gives a running story of the pathological process and that with present knowledge it is not suitable for use as a long range prognostic index. The data presented in this paper suggest the same thing. For instance, two cases out of 74 who had favorable leucocytic counts on discharge have had definite clinical and pathological relapses. It is true, however, that cases, regardless of the extent of the

disease, who develop favorable leucocytic reactions show a much lower percentage of casualties than do those who do not develop such a picture. It is possible that a long range prognostic index might be evolved were data available on a large number of cases who have been discharged for a period not shorter than five and preferably for ten years. This will however be a problem for the future. If such an index could be established it would prove to be a boon to many a tuberculous case.

One problem which it is necessary to investigate is the comparison of the clinical and the pathological interpretation of tuberculous cases. At present this is not possible with our data because sufficient time has not elapsed for a comprehensive clinical appraisal to be made. Consequently this article has been limited entirely to a discussion of the pathological problem.

In general, leucocytic responses are regarded as evidence of resistance on the part of the host to disease, especially those diseases caused by living microörganisms. The degree of response is taken to indicate the severity of the infection. In a case of pneumonia a moderate leucocytosis and neutrophilia is usually regarded as a favorable omen, whereas a marked leucopoenia or leucocytosis with or without neutrophilia carries with it a grave interpretation. Thus, it is the degree of change from normality that is of the greatest significance, even if all changes reflect a resistance of the host to his infection.

It is necessary to qualify still further the significance of the degree of alteration. Thus, in a case of pneumonia a leucocytosis of 20,000 and 90 per cent of neutrophiles is regarded as favorable whereas in a case of appendicitis it is considered as very serious. In these two instances the location and the nature of the pathological process receive their due attention. In other words, the pathogenesis of the disease process may markedly qualify the interpretation placed upon the leucocytic response.

The interpretations of leucocytic reactions presented in this communication have been qualified by the pathogenesis of the disease under consideration. The different phases of the pathological process, the chronicity of the lesions in both progression and regression, and the nature of the tissues involved have all had an important bearing upon the interpretation given. Whatever leucocytic picture found has been regarded as evidence of resistance to the tubercle bacillus infection, but the variety of reactions found could not all have the same significance. One does not question that the formation of a tuberculous abscess in the pulmonary tissue represents resistance of the host to the infection. But the rupture

of the abscess in such a tissue is of much more serious import than a similar condition located in the skin. In a similar way, it has been shown that leucocytic counts judged as favorable have a very different significance than those considered as very unfavorable even when the main seat of the pathology lies within the same type of tissue.

The author wishes to stress the point that the criteria used in the pathological analysis are arbitrary. The standards used may be found in time to be either too rigid or too lenient. Readjustments may have to be made as further facts come to light. The thing of greatest importance at present is not the exact standards but rather the concept by which leucocytic counts in tuberculous cases may be interpreted. The author feels that the soundness of this concept is substantiated by the *status quo* of the group of 281 tuberculous cases herein analyzed.

CONCLUSION

1. An analysis of 281 cases of pulmonary tuberculosis selected as clinically active is presented. This analysis is made on a pathological basis by use of consecutive leucocytic counts.

2. The pathological interpretation is compared with the status of the cases 1 to 5 years after discharge.

3. This comparison shows that the pathological interpretation is substantiated. The leucocytic reaction does indicate the trend of the underlying pathological process.

The author wishes to express his appreciation of the kindly cooperation of Drs. Ordway and Pesquera in the careful selection from clinical data of the group of cases used in this study. Also to Dr. A. J. Lotka for statistical analyses and for his interest in and criticism of the data submitted.

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CAVITIES IN PULMONARY TUBERCULOSIS

Their Relation to Mortality Rate and Duration of Life

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PART 1. MORTALITY RATE

This is a study of 1,962 series of chest roentgenograms of patients with pulmonary tuberculosis, to determine the incidence of cavity-formation and the relation of pulmonary cavities to the mortality rate and duration of life of the patient. These cases were admitted to Iola Sanatorium between March, 1918, when the first roentgenograms were made, and December 31, 1931, when this study was completed. Only those patients are included whose films are available and whose histories are complete; and, if dead, only those who died of tuberculosis.

Accurate information about the formation of cavities in pulmonary tuberculosis in the living patient has been available only since the application of the roentgen-ray to chest radiology. This covers a period of approximately twenty years. Previously, the physician depended entirely on physical examination of the chest in studying cavities. Information obtained in this way was unsatisfactory and inaccurate.

The most comprehensive report on cavity-formation and its relation to prognosis and duration of life in tuberculosis is by Barnes and Barnes (1), whose article has been widely quoted. In their series of 1,454 cases, the presence of cavities in the lungs was based on physical examination in 651 cases and on roentgenogological examination in the other 803. As the authors themselves point out, conclusions based on the first group are not entirely satisfactory. Among their conclusions are the following: The mortality rate increases and the duration of life of the patient decreases with an increase in number and size of cavities. Eighty-five per cent of all cavity cases are dead within fifteen years; the average duration of the dead cases of Barnes and Barnes often 15½ months from the time the cavity was discovered to date of death, and of both living and dead cases it was only two years up to the time of completion of their paper. From these findings, one would be safe in concluding that

[1] Iola Sanatorium, Rochester, New York.

cavity-formation in pulmonary tuberculosis carries a very grave prognosis.

Fishberg, in the last edition of his *Pulmonary Tuberculosis,* states, however, that

> a pulmonary cavity is proof that the organism is in possession of strong resisting powers, in fact, of immunity. Excepting the early round cavities, the hazard of tuberculous excavations varies inversely with the time it takes for their formation. The sooner they are produced, the worse is the outlook; the slower they develop, the better is the ultimate prognosis.

To Fishberg a cavity is ordinarily an indication of chronicity of the tuberculous process and does not necessarily mean a graver outlook for the patient.

In order to reach certain conclusions about the effect of cavitation on the life of the patient, the following aspects have been studied: Part 1, concerning the incidence of cavity-formation, the relation of the number, size and position of the cavities, and the relation of the sex and age of the patient to the mortality rate; and part 2, dealing with the relation of the same factors to the duration of life of the patient after discovery of cavitation by roentgenogram, and finally the effect of haemoptyses and thoracic surgery on both mortality rate and duration of life.

Evidence of cavity-formation was based entirely on the examination of the roentgenograms of each patient by the author, so that the interpretation or misinterpretation of annular shadows would be consistent throughout. Included in the series are a few patients who died in the sanatorium shortly after their admission and the only films available were taken after death. Life histories have been obtained from the sanatorium and dispensary records.

In general, the patients were divided into the living and dead, those with only one cavity on the first roentgenogram and those with two or more (multiple) cavities, and, finally, males and females. The duration of life was calculated in months from the first evidence of cavitation on the roentgenogram to the time of death or to December 31, 1931, if the patient were alive on that date.

INCIDENCE OF CAVITATION

In this series of 1,962 films studied, 1,601, or 80.6 per cent, had annular shadows interpreted to be cavities, at some time during the course of the disease. The remaining 361, or 19.4 per cent, had no definite roentgeno-

graphic evidence of cavitation. Cavities were present in 1,500 (93.6 per cent) of the cavity cases on the first roentgenogram taken in this sana-

TABLE 1

General summary of all cases

	CASES	PERCENTAGE
Total number of films studied	1962	
Total number of cavity cases	1601	80.6
Total number of males with cavities	917	57.2
Total number of females with cavities	684	42.8
Total number of single-cavity cases	505	31.5
Total number of multiple-cavity cases	1096	68.5
NUMBER AND PER CENT OF LIVING AND DEAD	**CASES**	**PERCENTAGE**
1. *Single cavity:*		
Males Dead	148	57.7
Living	109	42.3
Females Dead	119	47.9
Living	129	52.1
Total Dead	267	52.6
Living	238	47.4
2. *Multiple cavity:*		
Males Dead	457	69.3
Living	203	30.7
Females Dead	300	68.9
Living	136	30.7
Total Dead	757	69.1
Living	339	30.9
3. *Total cavity cases:*		
Males Dead	605	65.9
Living	312	34.1
Females Dead	419	61.2
Living	265	38.8
Total Dead	1024	63.8
Living	577	36.2

torium, while the other 101 developed cavities at some later date. Of the 1,601 cavity cases, 505, or 31.5 per cent, had only one cavity in the lungs

when cavitation was first discovered and 1,096, or 68.5 per cent, had two or more cavities. Males constituted 57.2 per cent and females 42.8 per cent of the cavity cases.

GENERAL MORTALITY RATE

The mortality rate for all 1,962 patients over a period of thirteen years and nine months was 56 per cent, that for cavity cases alone being 63 per cent and for noncavity cases 21.3 per cent. Single-cavity cases had a mortality rate of 53 per cent, as contrasted with 69.1 per cent for multiple-cavity cases. Males with cavities had a mortality rate of 65.9 per cent and females 61.2 per cent. Males with single cavities on the first roentgenogram had a rate of 57.7 per cent and with two or more cavities it was 69.3 per cent, while the females had, respectively, 48 and 68.9 per cent. Only in the group of females with a single pulmonary cavity did the living outnumber the dead and these only by a very small margin.

ANNUAL MORTALITY RATE

The mortality rate was computed on a yearly basis for the first five years after discovery of cavitation, while the second five and last four years were combined into two groups, due to the rapid decrease in the number of patients dying annually after the fifth year. Within the first twelve months after roentgenographic evidence of cavity-formation, 658, or 41.2 per cent, of all cavity cases were dead. By the end of the fifth year, 967 patients, or 60.3 per cent, had died, and at the end of fourteen years a total of 1,024 patients, or 63.8 per cent, were dead.

The 505 single-cavity cases had a mortality rate of 25.9 per cent at the end of the first year, 47.7 per cent at the end of the fifth, and 52.5 per cent at the end of the fourteenth year. The 1,096 multiple-cavity cases had mortality rates of 48.1, 66 and 68.9 per cent at the end of the first, fifth and fourteenth years, respectively. Examination of table 2 brings out the fact that the greatest difference in the mortality rates for these two groups of cavity cases occurred during the first year after discovery of excavation, after which time the mortality rate curves are more or less parallel.

Figures (not included) for the two sexes show that females with single pulmonary cavities had a slightly lower mortality rate for each year than did the males. At the end of the fourteenth year, 48 per cent of the females and 57.4 per cent of the males were dead. The mortality rates for females and males with two or more cavities were practically the

same for each of the fourteen years, 68.7 per cent of the females and 69.2 per cent of the males being dead at the conclusion of this study.

PERIOD OF SURVIVAL

The cases were divided according to the number of years they survived after cavities were first found on the roentgenogram and the percentage

TABLE 2

Annual mortality rate for 1,601 cavity cases

DURATION	NUMBER OF DEAD	PER CENT OF CASES	TOTAL PERCENTAGE
Total number of cases			
years			
1st	658	41.2	41.2
2nd	140	8.7	49.9
3rd	87	5.4	55.3
4th	55	3.4	58.7
5th	27	1.6	60.3
6–10th	52	3.2	63.5
10–14th	5	0.3	63.8
Single-cavity cases (505)			
1st	131	25.9	25.9
2nd	54	10.7	36.6
3rd	30	5.9	42.5
4th	19	3.7	46.2
5th	8	1.5	47.7
6–10th	22	4.3	52.0
10–14th	3	0.5	52.5
Multiple-cavity cases (1096)			
1st	527	48.1	48.1
2nd	86	7.8	55.9
3rd	57	5.2	61.1
4th	36	3.2	64.3
5th	19	1.7	66.0
6–10th	31	2.82	68.8
10–14th	1	0.09	68.9

of dead was determined for each year. Seven hundred and eighty patients (48.7 per cent) lived less than one year, 658 (84.5 per cent) being dead and the remaining 122 still alive on December 31, 1931. Two hundred and fifty-eight patients (16.2 per cent) lived between 25 and 36 months, and, of these, 140, or 54.5 per cent, died before December 31,

1931, the remainder being alive on that day. A decreasing number of patients survived for the third, fourth and fifth years, with a corresponding gradual decrease in the mortality rate for each year. Only 180 patients lived from five to ten years, 53 of whom were dead by 1931. Fifty-nine patients lived over ten years and only four (8.1 per cent) died before the completion of this study.

TABLE 3

Annual number of survivors and mortality rate

DURATION	NUMBER OF PATIENTS	PER CENT OF TOTAL	NUMBER DEAD	PER CENT OF COLUMN 1
		Single cavities		
years				
0–1	168	33.3	131	77.5
1–2	114	22.5	54	47.4
2–3	64	12.7	30	47.0
3–4	46	9.1	19	41.4
4–5	27	5.3	8	29.6
5–10	64	12.7	22	34.4
10–14	22	4.3	3	13.6
		Multiple cavities		
0–1	612	56.0	527	86.2
1–2	144	13.1	86	59.7
2–3	88	8.0	57	64.7
3–4	67	6.1	36	53.7
4–5	32	2.9	19	59.4
5–10	116	10.8	31	26.7
10–14	37	3.5	1	0.8
		Total		
0–1	780	48.7	658	84.5
1–2	258	16.2	140	54.5
2–3	152	9.5	87	57.3
3–4	113	7.0	55	48.6
4–5	59	3.7	27	45.8
5–10	180	11.2	53	27.9
10–14	59	3.6	4	8.1

Referring to table 3, we find that the number and percentage of patients surviving longer than one year are much higher for those with a single pulmonary cavity than for those with two or more cavities (66.6 per cent for the former and 44 per cent for the latter). There is a higher mortality

rate for each of the first five years for the multiple-cavity as compared with the single-cavity cases. The mortality rate of patients surviving beyond the fifth year was less for multiple-cavity cases than for those with single cavities.

SIZE OF CAVITY

The largest diameter of the cavity was measured in centimetres and, when two or more cavities were present, the diameter of the largest cavity was taken. Patients were classified according to the size of the cavity and the mortality rate was included for each size.

TABLE 4

Size of cavity

SIZE	NUMBER	PER CENT OF TOTAL	PER CENT DEAD
Single-cavity cases (505)			
cm.			
0–1	102	20.0	52.3
1–2	150	29.6	44.7
2–3	107	21.2	50.5
3–4	65	12.8	58.5
4–5	45	8.9	53.3
5–7	24	4.7	83.3
7–9	10	1.9	90.0
9 plus	2	0.3	100.0
Multiple-cavity cases (1096)			
0–1	97	8.8	53.6
1–2	225	20.6	52.0
2–3	229	20.9	66.8
3–4	212	19.3	69.2
4–5	119	10.8	78.0
5–7	137	12.5	83.9
7–9	56	5.1	93.0
9 plus	21	1.9	95.3

Distribution of the cases according to the size of the cavity in single-cavity cases shows that the largest number (150) had a cavity measuring 1 to 2 cm. Seventy and eight-tenths per cent of the 505 cases had a cavity measuring less than 3 cm. Only two patients had a single cavity over 9 cm. in diameter. The distribution for multiple-cavity cases showed that 229 (20.9 per cent) had the largest cavity measuring 2 to 3 cm. and 68.6 per cent of the cases had cavities measuring less than 4 cm.

in diameter. Only 21 patients (1.9 per cent) had cavities larger than 9 cm.

The mortality rate for single-cavity cases increased from 44.7 per cent for those with a cavity measuring 1 to 2 cm. to 100 per cent for the largest. Likewise, the mortality rate for the 1,096 multiple-cavity cases increased from 52 per cent with the largest cavity of 1 to 2 cm. in diameter for each increase in size to 95.3 per cent for those with the largest cavities. (See table 4.)

The sex of the patient played no part in the distribution of cases or in relation to the mortality rate.

Examination of table 5 for distribution of single-cavity cases according to period of survival, and table 6 for multiple-cavity cases, shows that after the first year of observation the expectancy of life in both groups decreased with each year as the size of the cavity or cavities increased. Likewise, the mortality rate increased correspondingly.

POSITION OF CAVITY

Cases with single cavities were distributed according to the third of the lung in which the cavity was situated (upper third from the posterior level of the 1st to the 4th ribs, middle third from the 4th to the 7th, and the lower third from the 7th to the 10th). Cases with two or more cavities were divided into those unilaterally and those bilaterally distributed. The unilaterally distributed multiple-cavity cases were further subdivided into those in which the cavities were limited to any one-third of the lung and those distributed through two or more thirds of either lung. Likewise, the bilaterally distributed cavities were subdivided into two groups: (1) when the cavities were limited to the upper thirds of both lungs and (2) when they were more extensively distributed.

Distribution of the 505 single-cavity cases showed that the largest number (51.2 per cent) had a cavity in the upper third of the right lung, followed by 33.6 per cent for the upper third of the left lung. The fewest number of cases had cavities in the lower third. Distribution for the multiple-cavity cases showed that 58.9 per cent of the 1,096 cases had cavities in both lungs. Thirty per cent had cavities widely distributed and the other 28.9 per cent had cavities limited to the apices. Of the unilaterally distributed cavities, 25.9 per cent had cavities limited to one-third of one lung and 14.9 per cent distributed over two-thirds or more of one lung.

The mortality rate for single-cavity cases was highest for those patients

TABLE 5

Size of cavity, single-cavity cases

Periods of survival and mortality rate

DURATION	NUMBER OF PATIENTS	PER CENT OF TOTAL	NUMBER OF DEAD	PER CENT OF COLUMN 1
Size of cavity, 1 cm.				
years				
0–1	30	29.4	22	73.3
1–2	17	16.6	7	41.1
2–3	21	20.5	9	42.8
3–4	12	10.7	4	33.3
4–5	5	4.4	1	20.0
6–10	15	14.7	9	60.0
11–14	2	1.9	1	50.0
	102			
Size of cavity, 2 cm.				
0–1	49	30.2	36	75.0
1–2	37	24.0	13	37.8
2–3	15	10.0	5	33.3
3–4	14	9.1	7	50.0
4–5	6	4.0	2	33.3
5–10	21	14.0	4	19.0
10–14	8	5.0	0	0
	150			
Size of cavity, 3 cm.				
0–1	34	31.8	25	73.5
1–2	32	29.9	18	56.2
2–3	10	9.3	4	40.0
3–4	9	8.4	2	22.2
4–5	5	4.6	1	20.0
5–10	9	8.4	2	22.2
10–14	8	7.4	2	25.0
	107			
Size of cavity, 4 cm.				
0–1	24	36.9	19	79.1
1–2	15	23.0	7	46.6
2–3	8	12.3	6	75.0
3–4	5	7.6	2	40.0
4–5	4	6.1	2	50.0
6–10	8	12.3	2	25.0
11–14	1	1.5	0	0
	65			

DURATION	NUMBER OF PATIENTS	PER CENT OF TOTAL	NUMBER OF DEAD	PER CENT OF COLUMN 1
Size of cavity, 5 cm.				
years				
0–1	8	17.7	7	87.5
1–2	9	20.0	5	55.5
2–3	7	15.5	4	55.5
3–4	4	8.8	3	75.0
4–5	6	13.2	1	16.6
5–10	9	20.0	4	33.3
10–14	2	4.4	0	0
	45			
Size of cavity, 5–7 cm.				
0–1	13	56.5	12	92.3
1–2	3	13.0	3	100.0
2–3	2	8.6	2	100.0
3–4	1	4.3	0	0
4–5	1	4.3	1	100.0
5–10	2	8.6	1	50.0
10–14	1	4.3	0	0
	23			
Size of cavity, 7–9 cm.				
0–1	7	63.6	7	100.0
1–2	1	9.9	1	100.0
2–3	1	9.9	0	0
3–4	1	9.9	1	100.0
4–5	0	0	0	0
5–10	1	9.9	0	0
10–14	0	0	0	0
	11			
Size of cavity, 9 cm.				
0–1	2	100.0	2	100.0
1–2	0	0	0	0
2–3	0	0	0	0
3–4	0	0	0	0
4–5	0	0	0	0
5–10	0	0	0	0
11–14	0	0	0	0
	2			

TABLE 6

Size of cavity, multiple-cavity cases

Periods of survival and mortality rate

DURATION	NUMBER OF PATIENTS	PER CENT OF TOTAL	NUMBER OF DEAD	PER CENT OF COLUMN 1
Size of cavity, 1 cm.				
years				
0–1	38	39.1	30	78.1
1–2	14	14.4	7	50.0
2–3	11	11.4	5	45.5
3–4	11	11.4	2	18.1
4–5	3	6.0	2	66.6
5–10	18	18.5	6	33.3
10–14	2	2.0	0	0
	97			
Size of cavity, 2 cm.				
0–1	112	49.0	80	71.4
1–2	31	13.3	16	51.6
2–3	18	8.0	9	50.0
3–4	10	4.0	4	40.0
4–5	8	3.5	4	50.0
5–10	33	14.6	4	12.1
10–14	13	5.7	1	7.3
	225			
Size of cavity, 3 cm.				
0–1	124	54.2	104	83.9
1–2	26	11.5	12	46.1
2–3	26	11.5	19	73.0
3–4	11	4.8	9	81.8
4–5	9	3.9	4	44.4
5–10	24	10.4	5	20.8
10–14	9	3.9	0	0
	229			
Size of cavity, 4 cm.				
0–1	111	52.3	101	90.9
1–2	36	16.9	20	55.5
2–3	18	8.5	10	55.5
3–4	13	6.1	7	61.6
4–5	7	3.3	5	71.4
5–10	22	10.0	8	33.3
10–14	5	2.3	0	0
	212			

DURATION	NUMBER OF PATIENTS	PER CENT OF TOTAL	NUMBER OF DEAD	PER CENT OF COLUMN 1
Size of cavity, 5 cm.				
years				
0–1	71	59.6	63	88.7
1–2	20	16.7	14	70.0
2–3	6	4.8	4	66.6
3–4	7	5.6	7	100.0
4–5	3	2.4	3	100.0
5–10	10	8.3	3	33.3
10–14	2	1.6	0	0
	119			
Size of cavity, 5–7 cm.				
0–1	94	67.6	86	91.3
1–2	13	9.2	13	100.0
2–3	9	6.4	8	88.8
3–4	10	7.1	5	50.0
4–5	3	2.1	1	33.3
5–10	6	4.3	3	50.0
10–14	4	3.6	0	0
	139			
Size of cavity, 7–9 cm.				
0–1	45	80.3	44	97.0
1–2	4	6.8	4	100.0
2–3	2	3.4	2	100.0
3–4	2	3.4	2	100.0
4–5	0	0	0	0
5–10	2	3.4	1	50.0
10–14	1	1.7	0	0
	56			
Size of cavity, 9+ cm.				
0–1	19	90.4	19	100.0
1–2	0	0	0	0
2–3	0	0	0	0
3–4	0	0	0	0
4–5	0	0	0	0
5–10	1	4.8	1	100.0
10–14	1	4.8	0	0
	21			

with a cavity in the middle third of the right lung (57.2 per cent); and then left middle, right upper, left upper, right lower; and finally lowest for the 7 patients with a cavity in the left lower third. The mortality rate for multiple-cavity cases was highest for those with bilaterally distributed cavities not limited to the apices, 80.4 per cent being dead. (A single dead case with cavities in the right lower third is of no clinical significance.) The mortality rate for cases with unilateral cavities limited to any two-thirds or more of one lung was higher than for bilat-

TABLE 7

Position of cavity and mortality rates

POSITION	NUMBER	PER CENT	PER CENT DEAD
Single-cavity cases (505)			
Right upper	258	51.2	54.5
Right middle	35	6.9	57.2
Right lower	8	1.5	37.2
Left upper	170	33.6	48.2
Left middle	31	6.1	57.0
Left lower	7	1.3	14.6
Multiple-cavity cases (1096)			
Right upper	147	13.4	55.6
Right middle	2	0.12	0.0
Right lower	1	0.09	100
Left upper	127	11.6	61.5
Left middle	7	0.6	43.0
Left lower	1	0.09	0
Right—more than 1/3	78	7.1	74.4
Left—more than 1/3	86	7.8	69.8
Bilateral—apical	317	28.9	66.3
Bilateral—not limited to apices	330	30.0	80.4

erally distributed cavities limited to the apices. The mortality rate for patients with two or more cavities in the upper third of either lung was only slightly higher than for patients with only one cavity similarly distributed. (See table 7.)

There was no material difference in distribution of the cavities or corresponding mortality rates for the two sexes. Also, there was no apparent relationship between the period of survival and the position of the cavities. As the period of survival increased, about the same percentage of patients died each year, irrespective of the position of the cavities,—with one exception, when only 20 per cent of patients with

extensively distributed bilateral cavities survived longer than one year, which is much lower than for any other group. (Tables not included.)

AGE OF PATIENT

The patients were divided according to age into five-year groups, from six to eighty, none being younger than six or older than eighty. The distribution of single-cavity cases showed that the number of patients increased rapidly with every additional five years from 0.9 per cent in the

TABLE 8

Distribution and mortality rates of single-cavity cases according to age of patients

AGE	MALES				FEMALES				TOTAL			
	Number of patients	Per cent	Number dead	Per cent of column 1	Number of patients	Per cent	Number dead	Per cent of column 1	Number of patients	Per cent	Number dead	Per cent of column 1
years												
0–5	0	0	0	0	0	0	0	0	0	0	0	0
6–10	0	0	0	0	5	2.0	3	60.0	5	0.9	3	60.0
11–15	5	1.9	5	100.0	19	7.6	6	31.7	24	4.7	11	46.0
16–20	25	9.8	12	49.0	41	16.5	23	56.0	66	13.0	35	53.0
21–25	49	19.0	24	49.0	55	22.1	29	52.6	102	20.2	51	50.0
26–30	27	10.5	12	44.5	52	21.0	23	44.4	79	15.6	35	44.3
31–35	37	14.4	23	62.1	30	12.2	13	43.3	67	13.5	36	53.6
36–40	28	10.8	17	60.7	13	5.2	7	53.8	41	8.1	24	58.5
41–45	16	6.2	8	50.0	5	2.0	2	40.0	21	4.1	10	49.0
46–50	32	12.4	21	63.6	11	4.4	6	54.5	43	8.5	27	62.8
51–55	15	5.8	10	66.6	8	3.2	3	37.5	23	4.5	13	56.5
56–60	9	3.5	6	60.0	3	1.2	1	33.3	13	2.5	7	53.8
61–65	5	1.9	3	60.0	3	1.2	2	66.6	8	1.5	5	62.5
66–70	7	2.7	6	86.0	1	0.4	1	100.0	8	1.5	7	87.5
71–75	1	0.3	1	100.0	1	0.4	0	0	2	0.3	1	50.0
76–80	0	0	0	0	0	0	0	0	0	0	0	0

6–10-year group to a maximum of 20.2 per cent for the 21–25-year group, after which there is a gradual decrease to the 71–75-year group. Similarly, the multiple-cavity cases showed an increase from 0.18 per cent for the youngest patients to a maximum of 17.5 per cent for those patients between 21 and 25 years, followed by a decrease to 0.27 per cent for patients over 75.

There is no apparent relationship between the age and the mortality rate for either single- or multiple-cavity cases. The only exception is for patients over 71 with multiple cavities, when the rate was 100 per cent (5 cases).

The distribution of cases is interesting when the two sexes are considered separately. In the single-cavity cases, 69.2 per cent of the females were between 6 and 30 years of age, while only 41.2 per cent of the males came within the same age limits. Likewise, in the multiple-cavity cases, 65.3 per cent of the females were 30 years or younger as compared to 34.6 per cent of the males. The mortality rate is slightly higher for females with a single pulmonary cavity at from 16 to 25 years and 60 to 70 years than for males; otherwise, the rate is uniformly higher for males. In the multiple-cavity cases, there is no uniform variation between the two

TABLE 9

Distribution and mortality rate of multiple-cavity cases according to age of patients

AGE	MALES (660)				FEMALES (436)				TOTAL (1096)			
	Number of patients	Per cent	Number dead	Per cent of column 1	Number of patients	Per cent	Number dead	Per cent of column 1	Number of patients	Per cent	Number dead	Per cent of column 1
years												
0–5	0	0	0	0	0	0	0	0	0	0	0	0
6–10	1	0.1	1	100.0	1	0.2	0	0	2	0.18	1	50
11–15	4	0.6	3	75.0	27	6.2	13	49.0	31	2.8	16	51.0
16–20	55	8.3	43	78.0	87	20.0	58	66.6	142	12.9	101	71.0
21–25	85	12.8	47	55.3	107	24.5	68	63.5	192	17.5	115	60.0
26–30	85	12.8	64	75.5	63	14.4	45	71.5	148	13.5	109	73.6
31–35	98	14.8	63	64.4	41	9.4	32	80.5	139	12.7	95	68.4
36–40	88	13.6	56	63.6	41	9.4	29	71.0	129	11.7	85	65.9
41–45	85	12.8	59	69.4	22	5.0	16	72.8	107	9.7	75	70.0
46–50	55	8.3	46	83.6	14	3.2	10	71.4	69	6.1	56	81.2
51–55	48	7.2	33	68.7	14	3.2	13	93.0	62	5.6	46	74.2
56–60	30	4.5	24	80.0	7	1.6	7	100.0	37	3.3	31	83.8
61–65	14	2.1	10	71.5	4	0.9	3	75.0	18	1.6	13	72.3
66–70	9	1.3	5	55.5	5	1.1	4	80.0	14	1.2	9	64.5
71–75	1	0.1	1	100.0	1	0.2	1	100.0	2	0.18	2	100.0
76–80	2	0.3	2	100.0	1	0.2	1	100.0	3	0.27	3	100.0

sexes. It is interesting to note that 78.3 per cent (47 patients) of 60 males between 6 and 20 years were dead as compared to 61.8 per cent (71 patients) of 115 females within the same age limit.

Except for the very old patients, the percentage of patients surviving each successive year is about the same for all age-groups in both single- and multiple-cavity cases. In the patients over 70 who have excavation, only one of eight survived longer than one year and that patient was still alive in 1931. Nor is there any connection between the mortality rate and period of survival. (Tables not included.)

CONCLUSIONS

After a study of the histories and serial roentgenograms of 1,962 tuberculosis patients admitted to Iola Sanatorium during a period of fourteen years, we can come to certain conclusions as to the effect of pulmonary cavities on the expectancy of life of the patient. Other factors, such as extent and type of disease, clinical signs, etc., enter into the general picture, but the conclusions here presented are based entirely on a study of cavities.

In our experience, we have found that the great majority of cases have cavities present at the first examination, and a comparatively small number develop cavities at some later date. Twice as many patients have two or more cavities than a single cavity when pulmonary excavation is discovered. Cavities appear as frequently in men as in women. The majority of the cavities (the largest cavity in cases when more than one is present) have a diameter of 5 cm. or less, the largest number in our series measuring between 1 and 2 cm. When only one cavity is present, it is more commonly found at the right than the left apex, in the middle thirds, and finally fewest at the bases. When two or more cavities are found on the roentgenogram, they are more commonly bilaterally distributed or, if unilaterally, then more often over two-thirds or more of one lung than limited to any one-third. There apparently is no age limit to the possibility of excavation, as the youngest subject was six and the oldest nearly eighty years old. The majority of cavity cases are between fifteen and forty years. The largest number of patients in any one five-year age-group in our series was in the twenty- to twenty-five-year group.

The mortality rate of cavity cases over a period of fourteen years is high,—66 per cent in this series (these including only deaths from tuberculosis and not from extraneous causes). The presence of two or more cavities carries a graver prognosis than one cavity. Since it was impossible in many cases to make an accurate count of the cavities, the cases were divided into two large groups, single and multiple cavities. As one would expect, the prognosis is influenced greatly by the size of the cavity or cavities,—the larger the cavity the graver the outlook, from our experience. Up to 5 cm., the size of the cavity in single-cavity cases apparently does not influence the death-rate.

The position of a single cavity does not influence the outlook greatly, although cases with a cavity in the middle third had a slightly higher mortality rate than in the upper or lower thirds. The presence of

multiple cavitation, limited to any one-third of either lung, does not carry a higher rate than for one cavity. However, as soon as cavities extend over two-thirds of one lung or are bilaterally distributed, the prognosis is worse, and, if widely distributed over both lung fields, the ultimate prognosis is very bad, our mortality rate for a large series of cases with this extensive distribution being 80 per cent during fourteen years and only 29 per cent of these having life-records longer than one year after discovery of the cavities.

The age of the patient has no apparent influence on the mortality rate except for the very old when nearly all over 70 are dead within one year after a cavity is found.

The sex of the patient is unimportant in relation to the size and position of the cavities and mortality rate. However, we did find that more than half of the females with pulmonary excavation were thirty years or under, while less than half of the males come within the same limits. Also, the mortality rate for young boys (15 to 20) with cavities was definitely higher than for girls of a similar age, although the actual number of girls was twice that of the boys.

Finally, the majority of cavity cases in a sanatorium will survive less than one year after the discovery of excavation, a decreasing percentage over a period of two years, etc., until comparatively few patients (3.6 per cent in this series) survive ten years or longer. The length of survival is influenced largely by the size of the cavity or cavities. The position of the cavities and the age of the patients do not have any apparent effect.

There seems to be no doubt that the presence of a cavity or cavities decreases the chances of ultimate recovery and possibility of survival for any prolonged period of time. While the mortality rates in this series are not as high as those of Barnes and Barnes, yet it forces one to the conclusion that two-thirds of all cavity cases will ultimately die of tuberculosis within fifteen years and the great majority will not live longer than five years.

SUMMARY

1. In a series of 1,962 cases of pulmonary tuberculosis, cavitation was found in 1,601, or 80.6 per cent, by roentgenographic examination.

2. On the first roentgenogram showing cavitation, a single cavity was found in 505, or 31.5 per cent, of the cavity cases, and two or more (multiple) cavities in 1,096, or 68.5 per cent. Males constituted 57.2 per cent of the cavity cases; females, 42.8 per cent.

3. The mortality rate for the cavity cases (deaths due only to tubercu-

losis) was 63.8 per cent over a period of 14 years, for single cavities 52.5 per cent, and multiple cavities 68.9 per cent. The mortality rate for all cavity cases at the end of the first year after discovery of cavitation was 41.2 per cent, after five years 60.3 per cent, and after ten years 63.5 per cent.

4. Forty-eight and seven-tenths per cent of the cavity cases were under observation one year or less, of whom 84.5 per cent died within that time; only 14.8 per cent survived five years, and 3.6 per cent of the total number of cases over ten years, with decreasing mortality rates for each year.

5. Of the 505 single-cavity cases, the largest number (29.6 per cent) had a cavity measuring 1–2 cm. in diameter, 70.8 per cent of the single cavities measured less than 3 cm., and 0.3 per cent over 9 cm. In the multiple-cavity cases, the largest number in any one group of cavity sizes was 20.9 per cent between 2 and 3 cm. in diameter (for the largest cavity), 68.9 per cent less than 4 cm. or less, and 1.9 per cent over 9 cm.

6. The mortality rate varied from 44.7 per cent for single-cavity cases of 1 to 2 cm. to 100 per cent for the largest; and for multiple-cavity cases from 52 per cent for cavities of 1 to 2 cm. in size to 95.3 per cent for the largest, with no significant variation for the sexes.

7. The location of single cavities shows 84.8 per cent in the upper thirds (51.2 per cent right, 33.6 per cent left), 13 per cent in the middle thirds, and 2.8 per cent in the lower thirds. Fifty-nine per cent of the cavities were located in the right lung; and 41 per cent in the left. The distribution of multiple-cavity cases was unilateral in 41.9 per cent and bilateral in 58.9 per cent.

8. The mortality rate for right upper-third single-cavity cases was 54.5 per cent, for left apex 48.2 per cent, and 57 per cent for the middle thirds and 35 per cent or lower for basal cavities. Bilateral cavitation carried a mortality rate of 73.2 per cent; unilateral multiple cavitation, 62.8 per cent. The highest rate, 80.4 per cent, was in those patients with widely distributed bilateral cavities.

9. The relation of age and cavity-formation showed that the largest percentage of single- and multiple-cavity cases in any one five-year age-group was between 21 and 25 years (20.2 per cent for the former and 17.5 per cent for the latter). Age limits in our series were from 5 to 80 years.

10. Mortality rates in relation to the age of the patient showed no consistent variation from one age-group to another except for those over 70 years, when it was 100 per cent.

11. The mortality rate for males and females was essentially the same

for both sexes, as far as size and distribution of cavities was concerned. However, the mortality rate for males twenty years or younger was 78.3 per cent, as compared to 61.8 per cent for females of similar age. Sixty-nine and two tenths per cent of females with single pulmonary cavities and 65.3 per cent with multiple cavitation were thirty years or younger, as compared to 41.2 and 34.6 per cent, respectively, for males of similar age.

I wish to express my thanks and appreciation to Dr. Ezra Bridge, Superintendent of Iola Sanatorium, for many helpful suggestions made during this study.

REFERENCE

(1) BARNES, H. L., AND BARNES, L. R. P.: Duration of life in phthisis with cavity, Amer. Rev. Tuberc., xviii, 412.

PART 2. DURATION OF LIFE

The influence of the number, size and position of cavities and of the age of the patient on the average duration of life of the tuberculosis patient is presented on a series of 1,601 cases of pulmonary tuberculosis with cavitation, admitted to Iola Sanatorium between March, 1918, and December 31, 1931. The effect of these factors on the mortality rate of this same group of patients has been presented in part 1 of this communication. In addition, the effect of haemoptyses and of thoracic surgery on the average duration of life has been computed.

In a series of 1,962 serial roentgenograms of patients with pulmonary tuberculosis, cavitation was found in 80.6 per cent. Of the cavity cases, 31.5 per cent had one cavity when excavation was first found on the roentgenogram, and the remaining 68.5 per cent had two or more cavities. Males constituted 57.2 per cent and females 42.8 per cent of the cavity cases. The mortality rate for all cavity cases over a period of fourteen years was 63 per cent, for cases with one cavity 53 per cent, and for those with two or more cavities 69.1 per cent. The mortality rate was shown to be influenced principally by the size of the cavity or cavities, and very slightly by either the position of the cavity in the lung, or the age of the patient, except in those of advanced years. Sex played a part in the mortality rate only when the age of the patient was considered.

The cases were subdivided into (1) the living and dead, (2) males and females, and (3) those with one cavity (on the first roentgenogram showing evidence of pulmonary cavitation) and with two or more cavities.

AVERAGE DURATION OF LIFE

The duration of life of each patient was computed in months from the date of discovery of pulmonary excavation on the roentgenogram to date of death or to December 31, 1931, if the patient were alive on that date (when this study was completed). The average duration of life is presented separately for the dead, the living and for both groups combined. Figures for the living patients naturally cannot be taken as conclusive and, although not entirely satisfactory, have been included for sake of completeness.

TABLE 10

Average duration of life in all cavity cases

	NUMBER DEAD	DURATION IN MONTHS	LIVING	DURATION	COMBINED	DURATION
Single cavity:						
Males	148	25.3	109	48.4	257	35.5
Females	119	22.7	129	39.4	248	31.5
	267	24.2	238	44.0	505	33.5
Multiple cavity:						
Males	457	13.5	203	49.4	660	24.6
Females	300	14.8	136	50.9	436	26.0
	757	14.0	339	50.1	1,096	25.1
Total:						
Males	605	17.6	312	48.5	917	28.4
Females	419	17.1	265	46.5	684	27.3
	1,024	17.4	577	47.5	1,601	27.8

The average period of life for 1,024 dead cavity cases is 17.4 months from the time the cavity was found to date of death. The 605 dead males lived half a month longer than 419 deceased females. The 267 dead with single cavities lived ten months longer than those 759 dead with two or more cavities, the former averaging 24.4 months and the latter group 14 months. Males with only one cavity in the lungs outlived the females of the same group by 2.6 months but, when two or more cavities were present, the females lived 1.3 months longer than the males.

Five hundred and seventy-seven patients alive on December 31, 1931, had an average of 47.5 months of life following the discovery of cavitation

by roentgenogram examination. An analysis of these cases is presented in table 10.

If all living patients had died on December 31, 1931, the average duration of life for the 1,601 dead and living cavity cases would have been 27.8 months of life, males living 1 month longer than the females, and patients with only one cavity living 8.4 months longer than those with two or more cavities.

SIZE OF CAVITY

The largest diameter of each cavity was measured in centimetres, and in the cases with two or more cavities, that of the largest cavity was recorded. The single and multiple-cavity cases were then subdivided into 7 groups according to the size of the cavity and the average duration of life for each group was computed (table 11).

In analyzing the figures for the dead patients, we found that, as a general rule, as the cavity increased in size the average duration of life decreased. In single-cavity cases, the patients with smallest cavity (up to 1 cm.) lived an average of 29 months as compared to 7 months for those with the largest cavity (over 9 cm.). Likewise, those patients with two or more cavities, all with cavities 1 cm. or less in size, lived 20.9 months in contrast to 5.8 months for those with cavities over 9 cm.

The average duration of life of the living patients varied greatly, with no apparent relationship to the size of the cavity or cavities. When the living and dead were combined, the figures simply confirmed the findings for the dead patients.

A comparison of patients with single and multiple cavities of a similar diameter in size showed that in every case those with multiple cavities lived a shorter time than those with only one cavity.

POSITION OF CAVITY

Single-cavity cases were divided into 6 groups according to the third of the lung in which the cavity was found, and multiple-cavity cases into those with unilateral distribution, limited to any one-third of either lung, or extending over two- or three-thirds.

Figures for the single-cavity dead patients showed the cases with a cavity in the lower third of either lung to have the largest average duration, but this, in part, is due to the small number of patients concerned. One patient with a cavity in the left lower third lived 85 months before he died, and three with cavity in the right lower third 29.6 months. Patients

with a cavity in the right middle third came next, followed by the left upper third, right upper third and, lastly, left middle third, respectively. When the living were combined with the dead, the same general relationship of the different lung areas was found except that the patients with a cavity in the right lower third lived longer than those with a cavity in the left lung similarly situated.

TABLE 11

Size of cavity and average duration of life

SIZE	DEAD		LIVING		COMBINED	
	Number	Average duration	Number	Average duration	Number	Average duration
			Single			
cm.		*months*		*months*		*months*
0–1	53	29.0	49	35.6	102	32.0
1–2	67	17.7	83	46.2	150	34.4
2–3	54	20.7	53	45.0	107	32.8
3–4	38	20.7	27	39.0	65	28.4
4–5	24	32.1	21	55.4	45	43.0
5–7	20	17.9	4	71.7	24	26.2
7–9	9	10.0	2	13.5	11	10.5
9 plus	2	7.0	0	0	2	7.0
			Multiple			
0–1	52	20.9	45	47.4	97	33.0
1–2	118	14.5	107	47.5	225	30.2
2–3	153	14.6	76	49.6	229	26.3
3–4	151	16.1	61	46.1	212	24.7
4–5	94	14.0	25	46.0	119	20.6
5–7	116	11.8	21	54.5	127	19.9
7–9	53	7.5	3	87.0	56	11.8
9 plus	20	5.8	1	130.0	21	11.7

When the tables for the multiple-cavity cases were analyzed, we found that dead patients with multiple cavities limited to the upper third of either lung lived longer than those with cavities more extensively distributed. Dead patients with cavities in the right upper third lived longest (20.4 months) followed by the left upper third, left middle third, and finally right lower third groups. Patients with cavities in two- or three-thirds of the right lung lived 1.2 months longer than the left lung cases. Those with cavities in the upper third of both lungs lived 0.8 months longer than those with right-sided cavities, and 6 months longer than

cases with cavities extensively distributed over both lung fields, the latter having an average span of life of only 9.9 months.

The figures for the different groups for the combined dead and living showed the same general relationship to each other as did the dead alone. Patients with multiple cavities in the right lung lived from 1.7 to 10.1 months longer than did those with cavities in the left lung.

TABLE 12

Duration of disease and position of cavity

LOCATION	DEAD		LIVING		COMBINED	
	Number	Average	Number	Average	Number	Average
Single						
		months		*months*		*months*
Right upper	141	22.5	117	47.2	258	32.6
Right middle	20	25.8	15	34.0	35	29.4
Right lower	3	29.6	5	57.6	8	47.0
Left upper	82	23.4	88	43.3	166	34.5
Left middle	20	13.4	11	30.0	31	19.3
Left lower	1	85.0	6	31.8	7	39.4
Multiple						
Right upper	82	20.4	65	56.4	147	36.2
Right middle	0	0	2	93.5	2	93.5
Right lower	1	1.0	0	0	1	1.0
Left upper	78	16.4	49	44.4	127	27.2
Left middle	3	12.3	4	31.5	7	23.2
Left lower	0	0	1	22.0	1	22.0
Right and left upper	210	15.8	107	49.2	317	27.0
Bilateral plus	265	9.9	65	35.8	330	15.0
Right lung	58	15.0	20	58.5	78	26.2
Left lung	60	13.8	26	46.4	86	24.5

AGE OF PATIENT

The single- and multiple-cavity cases were divided separately into five-year groups according to the age of the patient, from 6 to 80 years, the age limits in this series. The average duration of life for the single-cavity cases below 10 and over 61 was shorter than for any five-year group between those ages. Three dead patients between 6 and 10 averaged 12.6 months, and 13 dead over 60, from 11.2 months to 1 month (for the oldest case). Between 10 and 60, there was marked variation

in the number of months for successive five-year groups, 13.4 to 50.1 months, without any apparent relation to the age of the patient. Com-

TABLE 13

Duration of disease and age of patient

AGE	DEAD		LIVING		COMBINED	
	Number	Average	Number	Average	Number	Average
			Single			
		months		*months*		*months*
6–10	3	12.6	2	27.0	5	18.2
11–15	11	15.7	13	43.4	24	30.6
16–20	35	19.3	31	35.0	66	26.6
21–25	53	21.3	51	50.0	102	36.0
26–30	35	21.1	44	51.5	79	38.4
31–35	36	33.0	31	43.4	67	37.5
36–40	24	13.4	17	70.5	41	41.0
41–45	10	13.5	11	34.4	21	24.4
46–50	27	23.1	16	36.0	43	27.9
51–55	13	30.4	10	43.6	23	38.1
56–60	7	50.1	6	35.1	13	43.3
61–65	5	11.2	3	32.6	8	19.2
66–70	7	7.7	1	18.0	8	9.0
71–75	1	1.0	1	30.0	2	15.5
76–80	0	0.0	0	0.0	0	0.0
			Multiple			
6–10	1	1.0	1	25.0	2	13.0
11–15	16	18.7	15	49.0	31	30.0
16–20	101	12.9	41	34.4	142	19.6
21–25	115	14.0	77	62.0	192	33.3
26–30	109	15.1	39	58.6	148	26.6
31–35	95	13.8	44	36.9	139	21.0
36–40	85	13.1	44	52.4	129	26.4
41–45	75	19.0	32	41.3	107	25.6
46–50	56	13.7	13	46.4	69	18.8
51–55	46	10.2	16	45.8	62	17.8
56–60	31	17.0	6	32.8	37	19.5
61–65	13	10.0	6	57.0	18	26.2
66–70	9	7.5	5	40.4	14	19.2
71–75	2	2.5	0	0	2	2.5
76–80	3	3.0	0	0	3	1.0

bining the living and dead cases did not alter the general relationship of one group to another.

In considering patients with two or more cavities, we found that one

dead patient less than 10 years old lived one month, while 27 dead patients over 60 lived from 10 to 2.5 months. Five patients over 70 had an average of only 1.8 months before death. Between 10 and 60 years of age, the average duration of life for each five-year group varied from 10.2 to 19 months, with no relation to the age of the patient. Again, figures for the combined living and dead again did not alter greatly the relation of one group to another.

EXCAVATION AFTER FIRST ROENTGENOGRAM

Patients whose first roentgenograms showed no evidence of cavitation but who developed cavities at some later examination numbered 101, or

TABLE 14

Cavitation occurring after first roentgenogram

	NUMBER OF CASES	AVERAGE DURATION OF LIFE AFTER DISCOVERY OF CAVITY	NUMBER OF MONTHS ELAPSING BETWEEN DATE OF FIRST FILM AND CAVITATION	AVERAGE NUMBER OF X-RAYS TAKEN BEFORE CAVITY FORMATION
		months		
Dead:				
Males	34	16.2	17.2	2.9
Females	25	10.8	22.4	3.2
Total	59	13.9	19.3	3.0
Living:				
Males	13	24.4	14.6	2.2
Females	29	29.4	28.5	3.8
Total	42	27.8	24.2	3.3
Total	101	19.7	21.4	3.1

6.3 per cent, of the 1,601 cavity cases. All the others had cavities present on the first roentgenogram. Of these 101 cases, 59, or 58.4 per cent, were dead, and 42, or 41.6 per cent, living. The time elapsing between the first roentgenogram and the first to show cavitation averaged 21.4 months for the total number of cases, 19.3 months for the dead, and 24.2 months for the living. An average of 3 films was taken before cavities were found. The average duration of life after cavitation was found was 19.7 months for all cases, 13.9 months for the dead, and 27.8 months for the living.

This group of cases included 47 males and 54 females; by the end of 1931, 72 per cent of the males and 42 per cent of the females were dead. The dead males lived 5.4 months longer than the females.

HAEMOPTYSIS

A history of an haemoptysis of a dram or more was obtained in 517, or 32.2 per cent, of the cavity cases. Seventy per cent of the 517 were dead by the end of 1931. Fatal haemoptyses occurred in 20 cases, (1.25 per cent of the cavity patients).

Of the males 34.7 per cent gave a history of haemoptysis as compared to 29.3 per cent of the females. Seventy-four per cent of the males and 62 per cent of the females who had had haemoptyses were dead. Of the fatal haemoptysis cases, 12 were males and 8 females.

TABLE 15

History of haemoptysis

	NUMBER	AVERAGE DURATION OF LIFE
		months
Dead:		
Males	237	21.0
Females	125	21.2
Total	362	21.2
Living:		
Males	81	60.5
Females	74	49.7
Total	155	55.3
Total number of cases	517	31.4

The 362 dead haemoptysis cases had an average duration of life of 21.2 months; 237 males 21 months, and 125 females 21.5 months. The 155 living haemoptysis cases had an average of 55.3 months each at the end of 1931; the 81 males 60.5 months, and 74 females 49.7 months. The average duration of life for both living and dead was 31.4 months, which is four months greater than for the average duration of life for all cavity cases.

THORACIC SURGERY

During fourteen years, 275 of the 1,601 cavity cases had been subjected to some form of chest surgery. This included 156 cases of artificial pneumothorax (successful, in that some degree of collapse was obtained), 178 cases of phrenicoexairesis, 18 cases of temporary block of the phrenic nerve, and 22 cases of thoracoplasty or of rib resection (for tuberculous empyema). Many of the 275 patients had more than one type of operation, a few having as many as four during the course of the disease.

Eighty-six patients who had operations were dead by the end of 1931. One-half of these are included in the single-cavity group, the other half having two or more cavities. The 43 operated cases with single cavities had an average duration of life of 27.8 months, one month longer than the nonoperated cases of the same group. Those operated cases with multiple cavities averaged 25.5 months, which was 12.5 months longer than for the nonoperated patients. The 86 dead operated cases lived 10 months longer than did the 938 dead nonoperated patients.

TABLE 16

Comparison of operated and nonoperated dead cavity cases

	OPERATED		NONOPERATED	
	Average number	Average duration	Average number	Average duration
Single				
Males	24	29.9	124	30.2
Females	19	25.0	100	22.3
Total	43	27.8	224	26.8
Multiple				
Males	23	21.2	434	13.1
Females	20	30.6	280	13.7
Total	43	25.5	714	13.4
Combined single and multiple				
Males	47	25.6	558	17.0
Females	39	27.9	380	16.0
Total	86	26.7	938	16.5

It is impossible to compare the 186 operated cases who were alive on December 31, 1931, with the 388 nonoperated living cases, as their life histories were not complete and the full effect of surgical interference cannot be properly evaluated until all are included among the dead. The average duration of life for the nonoperated was greater than for that of the operated, because of the fact that the majority of the latter were more recent admissions and not a few of the former had lived a number of years with cavities present in the lungs.

The two sexes, dead and living, showed only slight differences in the average duration of life for both groups of cases, operated and non-

operated. Males constituted 42 per cent of the operated cases; females 58 per cent.

SPUTUM EXAMINATIONS

A positive sputum was found in 89 per cent of the 1,601 cavity cases and negative sputum in 5.9 per cent, while no sputum was obtained for examination in 5.1 per cent. A higher percentage of the dead had a

TABLE 17

Comparison of operated and nonoperated living cavity cases

	OPERATED		NONOPERATED	
	Average number	Average duration	Average number	Average duration
Single				
Males	33	35.0	76	56.2
Females	65	35.9	64	43.0
Total	98	35.9	140	50.2
Multiple				
Males	38	48.8	165	60.5
Females	64	36.4	83	53.5
Total	91	47.6	248	58.2
Combined				
Males	71	41.8	241	59.2
Females	118	40.8	147	49.0
Total	189	41.5	388	55.6

positive sputum than did the living (91 per cent for the former *vs.* 85.3 per cent for the latter). There was no marked difference in the percentage for males and females for any type of sputum.

CONCLUSIONS

The effect of the number, size and position of cavities and the age and sex of the patient on the average duration of life in 1,601 tuberculous cavity cases has been analyzed. We have found that the two principal factors influencing the life of the patient have been number and size of the cavities. Those cases that had two or more cavities present on the first roentgenogram showing evidence of cavitation had an average of

25.1 months as compared to 33.5 months for those with only one cavity, a difference of 8.4 months. If the dead are considered alone, then the difference was slightly greater, 10.2 months. The average duration for all cavity cases was found to be 27.8 months (to December 31, 1931) and for the dead only, 17.4 months.

As the cavity or cavities increased in size, the duration of life of the patient decreased (with two minor exceptions in single-cavity cases) for both groups of cavity cases. The greatest average duration in single-cavity cases was for those with a cavity 1 to 2 cm. in diameter (34.4 months) with an almost steady decrease to the shortest period for those with a cavity over 9 cm. (7 months). When two or more cavities were present, the smallest cavities allowed the patient a span of life of 33 months and the largest only 11.7 months.

TABLE 18

Sputum examinations

	POSITIVE	PER CENT	NEGATIVE	PER CENT	NO SPUTUM OR NO EXAMINATION	PER CENT
Dead:						
Males	558	92.0	22	3.6	25	4.1
Females	374	89.2	24	5.7	21	5.0
Total	932	91.0	46	4.5	46	4.5
Living:						
Males	267	85.5	24	7.7	21	6.7
Females	225	85.0	25	9.4	15	5.6
Total	492	85.3	49	8.5	36	6.2
Total	1,424	89.0	95	5.9	82	5.1

It was found that patients with cavitation in the right lung had a longer average duration of life than did those with left-lung cavities; with one exception, cases with a single cavity in the upper third when those with a cavity on the left outlived those on the right by a few months. Patients with multiple cavities did not live as long as those with only one cavity. Cases with cavities in both upper thirds lived slightly longer than cases with cavities in one lung only (two- or three-thirds of the lung being involved), and the latter lived longer than those with bilateral cavities of extensive distribution.

The age of the patient at the time cavitation was found did not influence

the average duration of life greatly, except for those between 6 and 10 and over 60 years, when the span of life was shorter than for any five-year group between those ages.

Males had a 1.1 months' longer average duration than did females. The difference for the dead cases was 0.5 months and for the living 2 months, each time in favor of the males. Males with single cavities lived 4 months longer than females, but with multiple cavitation 1.4 months less.

The figures, in the main, substantiate those of Barnes and Barnes (1) in their analysis of 1,454 cavity cases. They found that right-sided cavity cases lived longer than did left-sided cases, and that the increase in both number and size of the cavities adversely affected the average duration of life of the patient. Their average duration for dead cases was 15.8 months as compared to 17.4 months and for all cases 24 months in contrast to 27.8 months for our series. Tables were not presented showing the effect of age on duration of life.

Apparently the development of pulmonary cavitation following the first roentgenographic examination which had no evidence of cavitation carried an unfavorable prognosis, as 59 dead cases lived only 13.9 months as compared to 17 months for all dead cavity cases and 42 living cases 27.8 months in contrast to 47.9 months for all living cavity cases. The dead were under observation a period of 19 months and the living 2 years before excavation was discovered, with an average of 3 examinations per patient during that time. The majority of these cases were being treated outside the sanatorium when cavitation was found.

A history of haemoptysis was found in 32 per cent of the cavity cases. These patients lived 4 months longer than did all cavity cases, the dead 3.8 months, and the living 7.6 months. Fatal haemoptyses occurred in 20 cases (1.25 per cent). Six per cent more males gave a history of haemoptysis than did females.

In spite of the fact that cases of choice were not separated from those of necessity, it was found that chest surgery (including all types) increased the life of 86 dead patients by ten months. It was impossible to compare the effect of surgery on patients who were still alive on December 31, 1931, as their life histories were not complete. Barnes and Barnes likewise found that chest surgery (restricted to artificial pneumothorax in their series) "greatly improved the outlook."

Barnes and Barnes found tubercle bacilli in 99 per cent of their cases with cavities over 2 cm. We found positive sputum in 89 per cent of all

cavity cases, and a negative sputum in 5.9 per cent. No sputum was obtained in the remaining 5.1 per cent (82 cases).

SUMMARY

1. The average duration of life of 1,024 dead pulmonary-tuberculosis patients with cavitation from time of discovery of the cavities by roentgenogram examination to date of death was 17.4 months, of 577 living patients up to December 31, 1931, 47.5 months, and of the combined groups 27.8 months.

2. Nine hundred and seventeen males, living and dead, averaged 28.4 months, 684 females 27.3 months, 505 single-cavity cases 33.5 months, and 1,096 multiple-cavity cases 25.1 months.

3. The larger the diameter of the cavity, the shorter was the average duration of life.

4. With one exception, right-sided cavity cases lived longer than left-sided cavity cases. Patients entering with cavities widely distributed throughout both lungs had the shortest duration of life.

5. Except for the very young and very old, there was no apparent relation between age and average duration of life of cavity cases.

6. One hundred and one cases excavated after the first film showed no evidence of cavitation. These cases lived 8 months shorter than did all cavity cases, with a mortality rate of 58.4 per cent.

7. Five hundred and seventeen living and dead cases giving a history of haemoptysis lived on the average of 5.4 months longer than did 1,084 cavity cases with no history of haemoptysis.

8. Eighty-six dead cavity cases with history of some form of chest surgery lived 10 months longer than 938 nonoperated cases.

9. Positive sputum was found in 89 per cent of all cavity cases, and negative sputum in 5.9 per cent, and no sputum was obtained for examination in 5.1 per cent.

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THE TREATMENT OF PULMONARY TUBERCULOSIS BY HYPERPYREXIA

3. Temperatures that Inhibit Growth of Cultures of Mammalian and Avian Tubercle Bacilli and one Strain of Leprae Bacillus

A Method of Typing Suggested[1]

G. R. DUNCAN[2] AND E. S. MARIETTE[2]

It has previously been reported by us that there is a difference in the type of tubercle bacillus that causes progressive disease in various species of domestic animals as the temperature range varies. The human type of tubercle bacillus causes progressive disease in domestic animals of relatively low temperature but not in those animals of relatively moderate- and high-temperature range. The bovine tubercle bacillus causes progressive disease in animals of relatively low- and moderate-temperature range. In animals of high-temperature range, progressive disease is always caused by the avian tubercle bacillus (1).

We have treated 19 cases of pulmonary tuberculosis by artificial hyperpyrexia through the media of baths and general diathermy. Sixteen cases have shown X-ray improvement. Two cases have shown no change and one case has become worse. This case was going down hill all through residence before treatment. All the other cases are far advanced and were not doing particularly well before treatment. Seven of the cases have had their outlook definitely improved by treatment. One extra-pulmonary case, typed human, had been treated and has shown improvement. One case, improved by treatment, is now dead as the result of a rupture of an empyema pocket through his lung and cardiac failure. The reason for the selection of pulmonary tuberculosis cases is that the large majority of these cases are of the human type. Park and Krumwiede collected 644 cases of pulmonary tuberculosis typed human to one bovine case (2). The X-ray improvement is sometimes only very slight in longstanding fibroid cases but is marked in more recent cases.

Besides the work on domestic animals and patients, we now offer

[1] Presented at the Thirtieth Annual Meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 15, 1934.

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further argument by experiments with cultures in favor of the detrimental effect of heat on growth of the human type of tubercle bacillus.

Eight incubators were kept at 96, 98, 100, 102, 104, 106, 108 and 110°F. by the use of thermostats and standard thermometers. Thirteen strains of acid-fast pathogenic bacillus were used in the experiment; five strains of human, five strains of bovine, and two strains of avian tubercle bacillus, and one strain of leprae bacillus. Three cultures of each strain were put in each incubator following transplantation from their respective mother cultures. A loopful of culture was used for each transplantation. When sufficient time had elapsed (ten days with the leprae culture to four weeks with some of the bovine strains) the cultures were taken from the incubators and checked for gross evidence of growth. Photographs were taken of each series of three tubes immediately after transplantation, but before incubation, and of these same tubes following incubation. The careful comparison of these photographs helped to accurately determine growth of the cultures. Four of the human and one of the bovine strains were isolated and typed by Dr. Van Winkle from Glen Lake Sanatorium patients.

Protocols

Case 1: Human; F. P. Patient at Glen Lake Sanatorium. Pulmonary tuberculosis, F. A. (b), tuberculosis of right wrist. Died in residence. Specimen right wrist 12/30/32. Typed through guinea pig, culture, and two rabbits, 5/4/33, as human. Twenty-four tubes of glycerine-egg media transplanted 8/14/33. Generation eight. Incubated, three tubes per incubator, until 9/4/33 (3 weeks).

Case 2: Human; strain H-37. Received from Dr. L. U. Gardner, Saranac Lake 7/1/33. Twenty-four tubes of glycerine-egg media transplanted 8/14/33. G. L. S. generation three. Incubated, three tubes per incubator, until 9/4/33 (3 weeks).

Case 3: Human; M. N. Patient at Glen Lake Sanatorium. Pulmonary tuberculosis, F. A. (b), tuberculosis of right knee, genitourinary tuberculosis. Died in residence. Specimen from right knee, 7/12/33, grown directly on culture. Typed through two rabbits 12/28/33 as human. Twenty-four tubes of glycerine-egg media transplanted 9/25/33. Generation six. Incubated, three tubes per incubator, until 10/16/33 (3 weeks).

Case 4: Human; E. O. Patient at Glen Lake Sanatorium. Pulmonary tuberculosis, M. A. (a), genitourinary tuberculosis. Specimen from left ureter 4/19/33. Typed through guinea pig, culture, and two rabbits, 12/28/33, as human. Twenty-four tubes of glycerine-egg media transplanted 9/27/33.

Generation six. Incubated, three tubes per incubator, until 10/19/33 (3 weeks).

Case 5: Human; T. W. Patient at Glen Lake Sanatorium. Nonclinical pulmonary tuberculosis. Sinus tracts extending over left chest-wall, and down left side to leg, apparently the result of an old empyema puncture wound. Specimen from tract in leg 1/17/33. Typed through guinea pig, culture, and two rabbits, 7/6/33, as human. Twenty-four tubes of glycerine-egg media transplanted 10/14/33. Generation nine. Incubated, three tubes per incubator, until 11/4/33 (3 weeks).

Case 6: Bovine; E. K. Pleural effusion; tuberculous spondylitis of 11th and 12th dorsal vertebrae. Specimen from paravertebral abscess, 1/16/33. Typed through guinea pig, culture, and two rabbits, 6/13/33, as bovine. Unfortunately this culture was allowed to die out during the summer of 1933. A guinea pig was reinjected from material from the same abscess, 9/27/33, and grown in pure culture. This we believe for all practical purposes may be considered bovine, although a second typing was not done. Twenty-four tubes of glycerine-egg media transplanted 1/6/34. Generation four. Incubated, three tubes per incubator, until 1/27/34 (3 weeks).

Case 7: Bovine; received from Dr. Larson, University of Minnesota, 7/26/33, who had received culture from Dr. Van Es. Twenty-four tubes of glycerine-egg media, transplanted 8/15/33. G. L. S. generation two. Incubated, three tubes per incubator, until 9/5/33 (3 weeks).

Case 8: Bovine; received from Dr. Fitch, University Farm School, 9/21/33, who received culture from Dr. Feldman. "Bovine 1326 was isolated in April, 1932, from a mediastinal lymph node of a bovine slaughtered in Chicago." Twenty-four tubes of plain egg media, transplanted 10/15/33. G. L. S. generation two. Incubated, three tubes per incubator, until 11/12/33 (4 weeks).

Case 9: Bovine; received from Dr. Fitch, University Farm School, 9/21/33, who received culture from Dr. Feldman. "Bovine 438 was isolated in May, 1929, from a lung lesion of a four-year-old Holstein." Twenty-four tubes of plain egg media transplanted 10/19/33. G. L. S. generation two. Incubated, three tubes per incubator, until 11/16/33 (4 weeks).

Case 10: Bovine; received from Dr. Fitch on 9/21/33, who received culture from Dr. Feldman. "Bovine 1301 was isolated in April, 1932, from a lymph node in a bovine slaughtered in Chicago." Twenty-four tubes of plain egg media transplanted 11/18/33. G. L. S. generation three. Incubated, three tubes per incubator, until 12/9/33 (3 weeks).

Case 11: Avian; received from Dr. Fitch on 9/21/33, who received culture from Dr. Feldman. "Avian strain 709 was isolated in 1928 from the liver of a chicken which originated near Algona, Iowa." Twenty-four tubes of glycerine-egg media transplanted 10/20/33. G. L. S. generation two. Incubated, three tubes per incubator, until 11/10/33 (3 weeks).

Case 12: Avian; received from Dr. Fitch on 9/21/33, who received culture from Dr. Feldman. "Avian 518 was isolated June, 1929, from the liver of a bird raised on a farm near Rochester." Twenty-four tubes of glycerine-egg media transplanted 10/27/33. G. L. S. generation two. Incubated, three tubes per incubator, until 11/17/33 (3 weeks).

Case 13: Leprae; received from Dr. J. Reichel, Mulford Biological Laboratories, Sharp and Dohme 9/25/33, one culture of M. Leprae #1629. Dr. R. J. Anderson describes this strain as one isolated from a human case of leprosy

RESULTS

Case No.	Type of Bacillus	Time of Incub.	Temperature of Incubators																					
			96°			98°			100°			102°			104°			106°			108°			110°		
			Tube Numbers																					
			1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
13	L	10 day	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	3+	4+	±	2+	3+
12	A	3 wk.	4+	4+	4+	4+	4+	3+	3+	4+	4+	4+	4+	3+	3+	2+	3+	2+	2+	2+	3+	3+	2+	1+	1+	2+
11	A	3 wk.	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	3+	2+	4+	3+	4+	4+	2+	0	±
10	B	3 wk.	2+	2+	2+	2+	2+	2+	1+	2+	1+	2+	2+	2+	±	2+	2+	1+	±	±	±	±	±	0	0	±
9	B	4 wk.	3+	3+	3+	2+	2+	2+	3+	3+	3+	2+	2+	±	1+	2+	0	0	0	0	±	±	0	0	0	0
8	B	4 wk.	3+	2+	3+	3+	2+	3+	2+	3+	2+	2+	2+	1+	1+	1+	1+	±	0	±	±	±	0	0	0	C
7	B	3 wk.	C	3+	3+	3+	3+	3+	4+	2+	3+	3+	3+	3+	3+	3+	3+	2+	2+	2+	2+	1+	1+	0	0	0
6	B	3 wk.	3+	4+	4+	4+	3+	4+	4+	3+	4+	3+	2+	4+	3+	2+	2+	2+	1+	±	±	1+	1+	0	0	0
5	H	3 wk.	4+	4+	2+	3+	±	4+	2+	2+	4+	±	0	±	1+	1+	±	0	0	0	0	0	0	0	0	0
4	H	3 wk.	3+	2+	2+	2+	2+	C	3+	3+	3+	3+	2+	1+	C	1+	1+	0	0	0	0	0	0	0	0	0
3	H	3 wk.	2+	3+	4+	3+	4+	C	2+	1+	4+	1+	1+	2+	±	0	1+	0	0	C	0	0	0	0	0	0
2	H	3 wk.	4+	4+	4+	4+	4+	4+	4+	4+	4+	3+	3+	3+	±	±	C	0	0	0	0	0	0	0	0	0
1	H	3 wk.	3+	3+	3+	3+	3+	2+	2+	3+	3+	±	1+	1+	0	0	0	0	0	0	0	0	0	0	0	0

4+ Very Heavy Growth
3+ Heavy Growth
2+ Moderate Growth
1+ Slight Growth
± Just Shows Growth
0 No Growth
C Contaminated

CHARTS BY HELMER GUNNARSON

FIG. I. CHART SHOWING GROWTH OF THE CULTURES IN THE VARIOUS INCUBATORS

in Honolulu, 1909. Twenty-four tubes of glycerine-egg media transplanted 10/13/33. G. L. S. generation two. Incubated, three tubes per incubator, until 10/23/33 (10 days).

The results are illustrated by the charts (figures I & II). All five human strains showed good growth up to and including the 100°F. incubator. Growth was scanty in the tubes in the 102 and 104°F. incubators. No growth was observed above 104°F. The bovine strains grew well up to and including the 104°F. incubator. Growth was scanty in the

tubes in the 106 and 108°F. incubators. In only one tube was there growth in the 110°F. incubator of the five groups of three tubes each. The two avian strains grew heavily to and including the 108°F. incubator. Growth was somewhat less in the tubes in the 110°F. incubator. M. Leprae grew well in all of the incubators.

The routine culture medium was Herrold's glycerine-egg medium, save with three of the bovine strains where the glycerine was omitted. One of the human strains was checked on glycerine-agar. The results were the same, although the growth was not as heavy as the same strain on glycerine-egg medium.

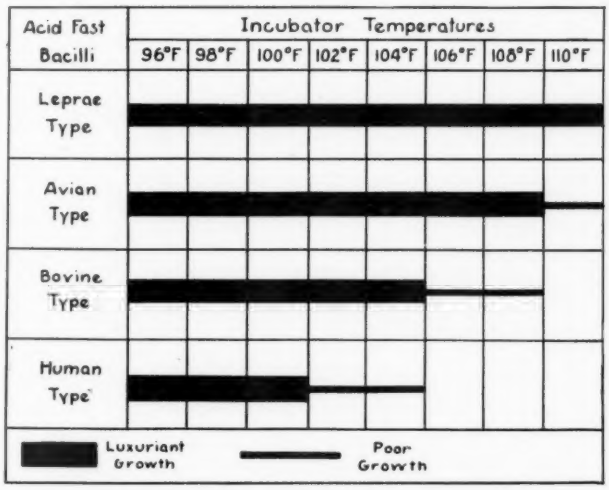
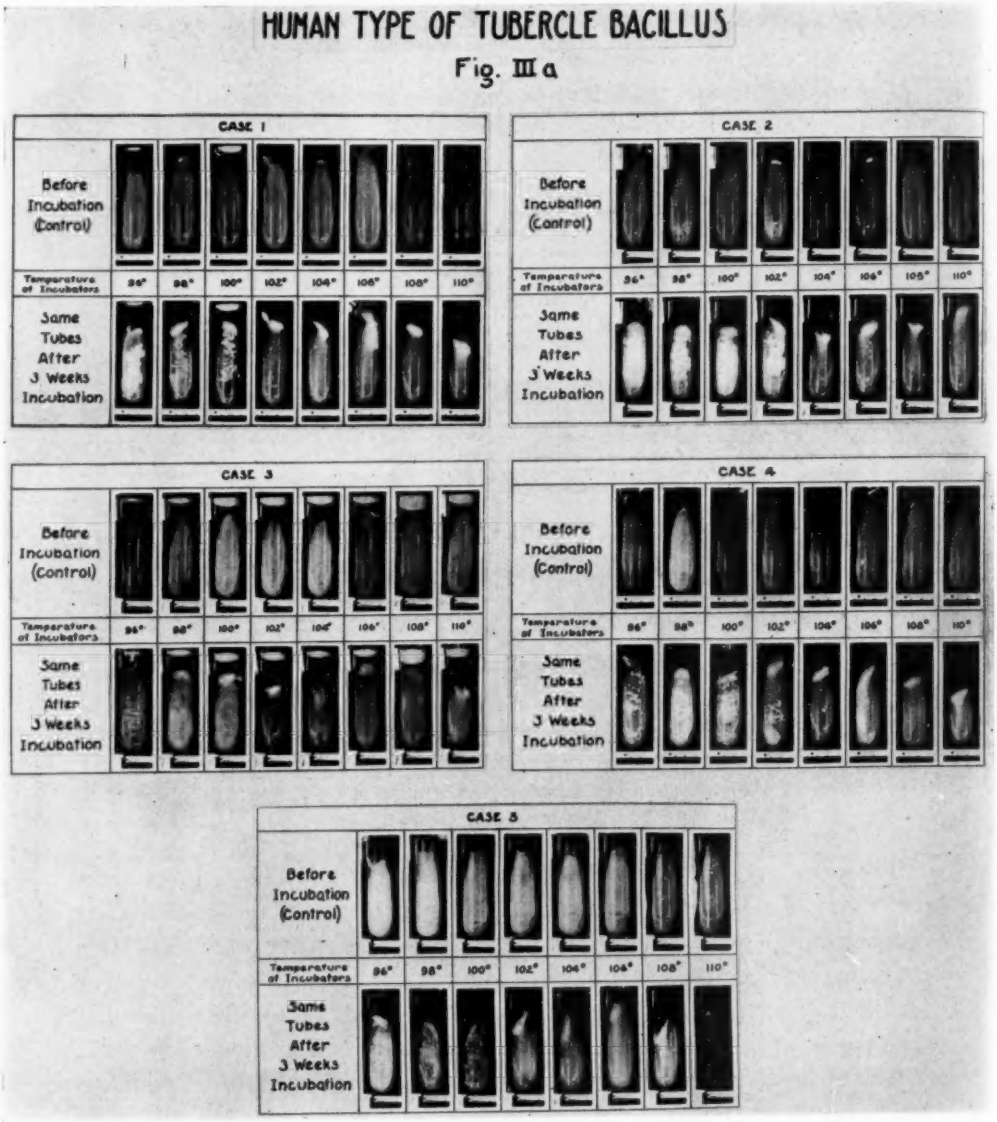


FIG. II. GRAPHIC SUMMARY SHOWING GROWTH OF THE CULTURES IN THE VARIOUS INCUBATORS

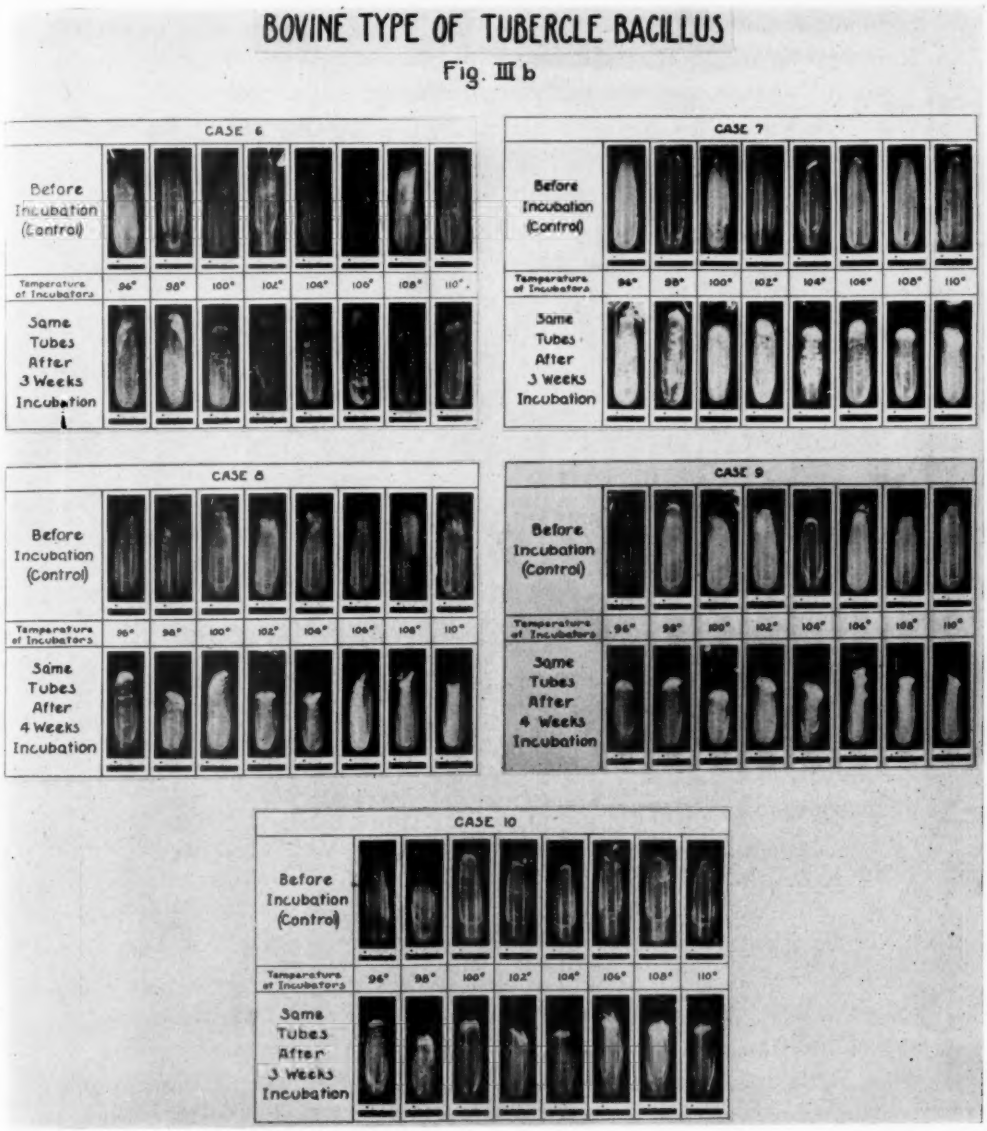
The photographic composites of the tubes (figures III a, b, c) show one series of tubes of each strain from each incubator before and after incubation. The tubes were numbered from 1 to 3 after transplantation for each strain for each incubator. When the photographs were selected for mounting, all tubes of the same number were taken. This somewhat eliminates arbitrary selection and presents a better general picture. With the bovine strains, growth was in some cases impossible to demonstrate by photograph, as the growth was a fine scum over the surface of the tube. Decision as to growth was made by scraping the surface of the tube with a platinum loop. In checking the photographs, the reader is warned not to confuse reflection of light on the slants or inoculum, that

appears unchanged in the control and incubated tubes, as growth. The leprae strain is red-orange in color and appears as black on the photograph.



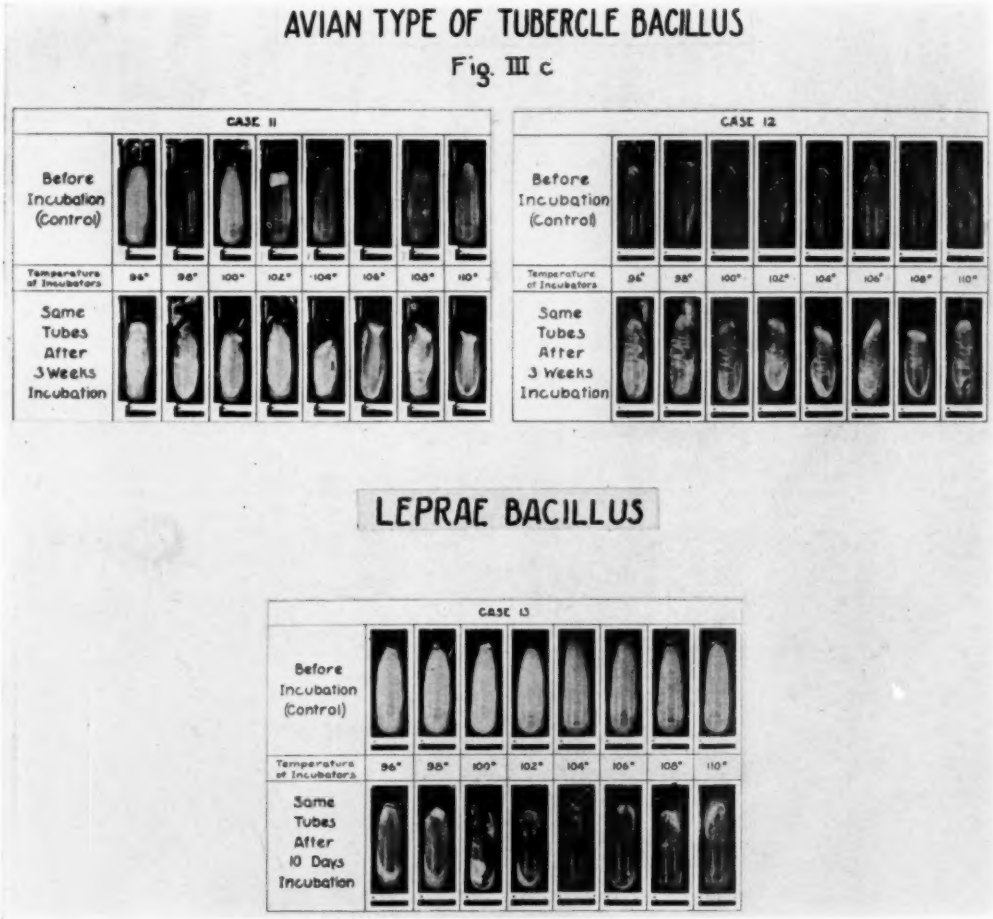
An attempt was made to determine what effect heating, in a manner similar to temperatures reached by hyperpyrexia patients, had on the growth of the human organisms. Nine culture tubes were inoculated

with strain H37. Three of these tubes were kept continually in the 98°F. incubator for controls. The remaining 6 tubes were kept in the 98°F.


BOVINE TYPE OF TUBERCLE BACILLUS
Fig. III b
CASE 6
Before Incubation (Control)
Temperature of Incubators
96° 98° 100° 102° 104° 106° 108° 110°
Same Tubes After 3 Weeks Incubation
CASE 7
Before Incubation (Control)
Temperature of Incubators
96° 98° 100° 102° 104° 106° 108° 110°
Same Tubes After 3 Weeks Incubation
CASE 8
Before Incubation (Control)
Temperature of Incubators
96° 98° 100° 102° 104° 106° 108° 110°
Same Tubes After 4 Weeks Incubation
CASE 9
Before Incubation (Control)
Temperature of Incubators
96° 98° 100° 102° 104° 106° 108° 110°
Same Tubes After 4 Weeks Incubation
CASE 10
Before Incubation (Control)
Temperature of Incubators
96° 98° 100° 102° 104° 106° 108° 110°
Same Tubes After 3 Weeks Incubation

incubator, save when one group of three tubes was put in the 102°F. incubator for one hour daily and the other group of three tubes was put in the 104°F. incubator for five hours twice a week. This process was

kept up for three weeks. All tubes showed heavy growth and one could not distinguish one from the other on this basis. Considering the fact that there are 504 hours in three weeks, and that the heating above 98°F. for one group was 21 hours total, and for the other group 30 hours total, it is not surprising that differences in growth could not be observed.


AVIAN TYPE OF TUBERCLE BACILLUS
Fig. III c
CASE 11
CASE 12
Before Incubation (Control)
Temperature of Incubators
96° 98° 100° 102° 104° 106° 108° 110°
Same Tubes After 3 Weeks Incubation
LEPRAE BACILLUS
CASE 13
Before Incubation (Control)
Temperature of Incubators
96° 98° 100° 102° 104° 106° 108° 110°
Same Tubes After 10 Days Incubation

This, we believe, emphasizes the fact that hyperpyrexia treatments are only of value if the patient has resistance to attack the organism over the relatively short time its growth is inhibited by treatment.

An experiment was run to determine whether or not two of the human strains (cases 4 & 5) were killed after three weeks incubation in the 106,

108 and 110°F. incubators. Photographs were taken at the beginning and at the end of the experiment to check growth. Four transplants of each of these two cultures were put in each incubator for three weeks. Following this, one of the four tubes was put directly back in the 98°F. incubator for three weeks; one tube was transplanted to two tubes of fresh media and these two transplants incubated at 98°F. for three weeks; the remaining two tubes were used to furnish 1 mgm. of organisms which were injected intraperitoneally into a guinea pig. The culture tubes of case 4, human, incubated for three weeks at 106° and 108°F. and then these tubes replaced in the 98°F. incubator for three weeks, showed slight but definite evidence of growth. The 110°F. culture, handled in the same manner, showed no evidence of growth. The culture tubes of case 5, human, handled as those of case 4, showed slight but definite growth when the 106°F. culture was reincubated at 98°F. but no growth following reincubation of the 108 and 110°F. cultures. Cases 4 and 5, cultures incubated at 106, 108 and 110°F. for three weeks, were transplanted and incubated at 98°F. for three weeks. There was no evidence of growth. One milligram of inoculum was collected from cases 4 and 5 culture tubes incubated at 106, 108 and 110°F. for three weeks. The inoculum was suspended in distilled water and injected intraperitoneally into guinea pigs. Case 4, 106°F.-incubated inoculum caused massive, disseminated tuberculosis in a guinea pig after 44 days. Case 4, 108°F.-incubated inoculum caused extensive tuberculosis of the spleen and mesenteric nodes with a few scattered tubercles in the liver and lungs of a guinea pig after 44 days. Case 4, 110°F.-incubated inoculum caused no gross tuberculosis in a guinea pig after 44 days. Case 5, 106°F.-incubated inoculum caused massive, disseminated tuberculosis and spontaneously killed the guinea pig after 44 days. Case 5, 108°F.-incubated inoculum caused a few discrete tubercles in the spleen and mesenteric nodes with no other gross evidence of tuberculosis in a guinea pig after 44 days. Case 5, 110°F.-incubated inoculum caused no gross tuberculosis in a guinea pig after 44 days.

To summarize: Cultures of two strains of human tubercle bacillus showed evidence of pathogenic activity after three weeks' incubation at 106 and 108°F., but none was demonstrated after three weeks' incubation at 110°F. The 106°F. strains caused more disease in guinea pigs than the 108°F. strains. Temperatures of 106° or 108°F. maintained for three weeks in man are at this time impossible. When we treat tuberculosis with hyperpyrexia, we are then probably dealing with a

thermal nongrowth point rather than a thermal death point as seen in gonorrhea (3) and syphilis (4).

It becomes evident from the preceding work that there is a difference in growth of the various types of tubercle bacillus when kept at different temperatures. We have shown in a preceding publication (1) that the type of tubercle bacillus causing progressive disease in domestic animals is related to the animals' normal temperature range. Animals with a temperature up to 100°F., or slightly higher, suffer progressive disease with the human and bovine types; from here to 104°F. or slightly higher, progressive disease is caused by the bovine type; and above this level to 108.5°F. (the high range of the fowl) progressive disease is of the avian type. Retrogressive lesions of the human type are found in animals with a temperature range from slightly above 100°F. to about 104°F. The heavy line of the summary chart of this culture work (figure I) indicates approximately the temperatures at which types of tubercle bacillus, causing progressive disease in domestic animals, change. Although from the growth and culture morphology one may gather some idea of the type of tubercle bacillus, still the criteria of typing to-day depends upon animal inoculation. Considering the fact that the effect of growth on the tubercle bacillus in culture is similar to the type of progressive disease seen in domestic animals, there is no particular reason why the culture method cannot be used for a determination of type. Three incubators, one at 100°F., one at 104°F., and one at 108°F. would be all that would be necessary.

The results may be tabulated as follows:

1. All five strains of human tubercle bacillus grew luxuriantly from 96° to 100°F. inclusive; poorly from 102° to 104°F. inclusive; and not at all above this temperature.

2. All five strains of bovine tubercle bacillus grew luxuriantly from 96° to 104°F. inclusive; poorly from 106 to 108°F. inclusive; and in only one tube out of fifteen at 110°F.

3. The two strains of avian tubercle bacillus grew luxuriantly from 96° to 108°F. and poorly at 110°F.

4. *M. leprae* (strain 1629, Mulford) grew luxuriantly from 96° to 110°F.

5. Two human strains, incubated for three weeks at 106 and 108°F., were still able to produce progressive disease in guinea pigs. These strains after three weeks' incubation at 110°F. caused no tuberculosis in 44 days in guinea pigs.

6. The temperature range at which cultures of various types of tubercle bacillus grow luxuriantly closely corresponds to the temperature range of domestic animals in which these organisms produce progressive disease. The temperature range at which cultures of various types of tubercle bacillus grow poorly closely corresponds to the temperature range of domestic animals in which these organisms produce nonprogressive chronic disease. The temperature range at which cultures of various types of tubercle bacillus do not grow includes generally the temperature range of domestic animals in which these organisms do not produce disease.

7. The work suggests a new and shorter method of typing.

We wish to acknowledge our indebtedness to Doctors Gardner, Fitch, Larson, Reichel, Feldman and Van Es for some of the cultures used in this work, and to thank L. Smith and H. Grandlund for their technical help.

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THE TUBERCULOSIS PROBLEM[1]

LEWIS J. MOORMAN[2]

A few decades ago the treatment of pulmonary tuberculosis was relatively simple. The accepted routine management consisted of rest in bed, fresh-air, light, sunshine, and good food, plus what often amounted to indifferent prophylaxis. The average family physician was familiar with the fundamental principles of routine management and accepted the obligation of treatment. Early or minimal cases usually did well under proper management; moderately advanced cases did less well; and advanced cases were often literally consumed by the disease. Though the physician was troubled by this obvious discrepancy in results, the therapeutic indications remained the same regardless of the character and stage of the disease.

Fortunately for those afflicted with the more advanced stages, the physician who makes a diagnosis of pulmonary tuberculosis to-day cannot intelligently project his therapeutic program until he has determined whether the case is minimal, moderately advanced, or advanced; whether it is acute or chronic; whether predominantly unilateral or bilateral. He must also recognize the presence or absence of cavities, and, if cavities are present, he must determine their size and location, the character of their walls, and the condition of the surrounding tissues. He must consider the pleura, and, if possible, determine the presence or absence of adhesions; he must ascertain the position and mobility of the diaphragm and the mediastinal structures; he must attempt at least a clinical estimate of the vital capacity of the lungs; he must appraise the cardiovascular system, with particular reference to the integrity of the heart muscle; he must recognize serious complications when present, as well as other associated pathological conditions.

These demands require unusual knowledge of the anatomy and physiology of the intrathoracic organs; an appreciation of the histopathology of tubercle from early proliferation to cavity-formation; special skill in

[1] Presented at the Clinical Section of the Southern Tuberculosis Conference, Knoxville, Tennessee, October 9, 1934.

[2] Oklahoma City, Oklahoma.

physical diagnosis, plus the wisdom of clinical experience, also fluoroscopic service and good stereoscopic X-ray films. Other laboratory facilities and occasionally additional highly technical procedures are needed.

There must be a choice between home treatment and institutional treatment. In those chosen for institutional treatment, there must be a choice between routine management and surgical collapse; in those chosen for surgical collapse there must be a choice between artificial pneumothorax, intrapleural and extrapleural pneumolysis, phrenic-nerve interruption or intercostal neurectomy, and thoracoplasty. Often there must be a decision with reference to simultaneous bilateral or successive bilateral pneumothorax; also with reference to cautious combinations of the various surgical procedures mentioned above. With all due regard for the skill and sympathetic understanding of the surgeon, the above decisions depend largely upon the clinician.

Modern advances in the treatment of pulmonary tuberculosis have brought a multiplicity of problems. It is obvious that the family physician cannot adequately meet all the above requirements. It is equally obvious that even those who specialize in diseases of the chest must resort to team work in order to accomplish the best results. It is unfair to both physician and patient to leave the management of pulmonary tuberculosis wholly in the hands of the family physician.

While there has been no change in our opinion with reference to the efficacy of the fundamental principles of treatment, rest, diatetic and hygienic, and while in certain cases these principles can still be successfully applied in the home environment, modern therapeutic advances, which have proved such a boon to those suffering from advanced tuberculosis, require the equipment and facilities of the sanatorium and the hospital. The minimal and moderately advanced cases not responding to routine management, and all advanced cases, require special diagnostic consideration in order to determine appropriate therapeutic measures. With rare exceptions, such diagnostic studies cannot be successfully pursued in rural communities. Neither is it possible to apply the respective modern therapeutic measures outside the well-ordered institution.

The above discussion makes obvious the fact that the difficulties are not only professional, but environmental as well. If these difficulties are not overcome, many of those suffering from tuberculosis will be denied the opportunities for recovery and many, who are not yet obviously tuberculous, will be unnecessarily exposed to infection. The true signifi-

cance of this situation can be vaguely sensed when we consider the fact that, of the 800,000 cases of pulmonary tuberculosis in the United States, 715,000 necessarily remain without institutional care. In all probability we are justified in assuming that the 85,000 available beds in the United States are not sufficient to care for all the advanced cases. Certainly the number of moderately advanced and advanced cases far exceed 85,000. It is the policy of some of our state institutions to refuse the admission of advanced cases. No doubt the majority of state sanatoria favor the admission of the less advanced cases.

Twenty-five hundred years ago, Hippocrates said: "The spitting of pus follows the spitting of blood, consumption follows the spitting of this, and death follows consumption." In the Second Century, A.D., Galen suspected the danger of contact and warned against it. In the middle of the 19th Century, Villemin, through inoculation, justified Galen's suspicion. In 1882, Robert Koch, proved what others had sensed, that the infectious microörganism is present in the sputum. With our modern diagnostic and therapeutic measures, is it not time for us to heed the teaching of Hippocrates and apply the knowledge now at hand? Evidently the dissemination of tubercle bacilli is in direct proportion to the quantity of sputum produced by those suffering from tuberculosis. If we assume there are 100,000 advanced cases of tuberculosis in the United States now engaged in the spitting of pus, and that they average two ounces of sputum daily, the result, in plain figures, would approximate six tons each day. Any attempt to estimate the number of tubercle bacilli in six tons of sputum would stagger all efforts at computation.

Our efforts to control the spread of tuberculosis are apparently unnecessarily inadequate, they are too apt to be sporadic and circumscribed, and wanting in comprehensive coördination. Sir Robert Philip, in an article entitled "The Principles Underlying a Scheme of Anti-Tuberculosis Measures in any Country," while giving credit for those forward strides resulting from continued observation and research, says:

> Yet it would appear that the practical significance of the scientific advance is still far from being sufficiently apprehended. Many meritorious efforts against tuberculosis have suffered because of failure to give one or other principle its proper place, or from imperfect correlation of the several principles. Men and women become fascinated by a particular corner of the field, and, in eagerness begotten of interest in the immediate work, lose sight of the larger outlines of the problem. Their corner of the field may be well tended; yet the value of the work is lessened because of lack of relationship to fundamental facts.

Certainly members of the medical profession have long been cognizant of the lack of wise application and comprehensive coördination of known facts and accepted methods of procedure.

In discussing the functions of the National Tuberculosis Association, Dr. Kendall Emerson, names the following as fundamental; (1) "The acquisition of knowledge about tuberculosis. (2) The dissemination and application of such knowledge."

With the above considerations in view, the author ventures to suggest the following program, which has grown out of his observation and experience over a long period of years in his own state, and which represents a consciousness of the inadequacy of the methods now employed. Since the tuberculosis problem is one which concerns public health, and its solution dependent upon proper administrative, professional, sociological, and economic factors, it would seem wise for the state to establish a non-partisan board for the purpose of formulating the policies and directing the agencies having to do with tuberculosis control. This board should be also endowed with authority to initiate and pursue a program which will aid the family physician in the diagnosis and proper management of tuberculosis in the home, and the placement of cases not suitable for home management.

Under the direction of such a board, state sanatoria should provide salaries sufficient to attract well-trained physicians, with a sympathetic understanding of the tuberculosis problem. With a thoroughly competent staff, the state institution should become a centre of education, not only for the patient, but for the members of the medical profession as well. The beds in the state sanatorium should be primarily for advanced cases. The turnover should be encouraged by adequate surgical treatment.

Through the offices of this board, affiliation with the state-university school of medicine should lead to a short period of residence in the state sanatorium for medical students in their senior year, in order that they might acquire a more comprehensive knowledge of the tuberculosis problem. Such an affiliation should also lead to the development of a tuberculosis department in the university, or teaching hospital, which would serve primarily as a clearing house for problem cases arising in the routine work of the state sanatoria and other agencies. The staff of this department, medical and surgical, with its highly refined diagnostic equipment and effective team work, including consultation service with all the specialties, should make final decisions and plans with reference to surgical collapse and bring about their execution under the most favor-

able conditions. In the author's opinion, transportation of even advanced cases is not hazardous, and chest surgery, with the exception of artificial pneumothorax, is best done in a general hospital, and not in a sanatorium. The most significant feature of such a coöperative plan is to be found in the educational advantages for nurses, medical students and interns.

The tuberculosis board should be empowered to establish tuberculosis county centres, or, in sparsely settled communities, district centres. Each centre to be in charge of a physician qualified by training and experience to direct and pursue tuberculosis control. Through such a medical director the work of the county or district centre and that of the state sanatoria, with their mutual interests, should be intimately identified with organized medicine. Everything possible should be done to enlist the interest of physicians through special conferences and through the arrangement of, and participation in, tuberculosis programs planned for regular sessions of the county or district medical societies and state medical associations. Such an affiliation should be welcome, since the purpose is to aid the family physician in the diagnosis and management of tuberculosis, and not to supersede, or replace, him; not to offer free medical service, but to attempt improvement of the medical service for which the usual fee is charged by the family physician.

In addition to this consultation service, each centre should be provided with adequate nursing service, which is to be primarily educational. Nurses are to be chosen not only with reference to their training in the care of the tuberculous, but with a view of their adaptability to the social and economic conditions in the respective communities, and their ability to teach. Their chief function should be the instruction of the patient with reference to the details of the therapeutic program under the direction of the tuberculosis consultant and the family physician. The nurses should also be charged with the instruction of the family in the care and prevention of tuberculosis. The nurses time should be primarily occupied in the proper alignment of new cases and periodic, unannounced visitations in the homes of patients already under treatment.

Tuberculosis centres should be closely identified with state and local tuberculosis agencies, and should aid in the general publicity program. They should virtually relieve these agencies of the responsibility of periodic clinics and case finding campaigns.

The advantages of such a plan might be enumerated as follows:

1: Controlled comprehensive coördinated administration, removed from political domination.

2: Adequate coöperative medical service. Carrying education to every doctor in the state; aiding in diagnosis and in home management, and selection of cases for institutional management; supplying valuable diagnostic and clinical data through the case-record, which always accompanies the patient; also providing the proper follow-up and treatment after the patient returns home.

3: Nursing service, which should be of inestimable value to the patient from a therapeutic and educational standpoint.

4: The combined professional and lay educational influences should succeed in making the community tuberculosis conscious, without the danger of phthisiophobia.

5: The prompt selective management of every discovered case should result in the control of a large percentage of active cases with the best prospects for arrestment or cure.

6: The breaking of contact by removal of advanced cases from the homes should materially lessen the danger of infection and reduce the number of potential cases of the adult type.

7: The reduction in cough and sputum in practically all cases under collapse therapy, and the disappearance of the tubercle bacilli in many, should naturally lessen the ultimate danger, even though contact is renewed.

8: The restoration of earning capacity and the consequent termination of the long financial drag in individual cases will go far toward compensating the necessary expenditures.

9: The resulting reduction in the incidence of the disease, in the duration of morbidity, and in the mortality rate, will ultimately reduce overhead costs, which should first become obvious in the institutions; because, under such a plan, the disease should seldom reach advanced stages except in the more recalcitrant cases.

10: Such a program as that proposed should create environmental conditions which, in the light of our present knowledge, would make preventoria and summer camps unnecessary.

11: The scientific care of a large number of cases in the home would render the ever-increasing demand for more institutional beds unnecessary and save the state or community, not only the heavy first cost, but maintenance as well.

12: The plan of keeping the management in the hands of the family physician, encouraging even the poor to pay something for services, would effect a great saving for the state, and obviate the serious danger of pauperizing a large number of people who should, on the other hand, be encouraged to maintain their self-respect.

13: This latter plan, coupled with a sliding-rate scale in the state institutions, in keeping with the patient's ability to pay, the maximum being commensurate with the fees charged in the average private sanatorium, would help to allay the growing fear of state medicine, and to some extent relieve over-burdened taxpayers. The nurse's economic and social survey would make such a fee-scale possible.

14: This plan should also prove invaluable from the standpoint of general public health and social well-being, thus reducing the sum-total of disability with a corresponding increase in earning capacity.

15: It is obvious that a summation of the material factors mentioned above should place this program on a sound financial basis.

16: Finally, according to our Hippocratic lead, consumption should be ultimately controlled by limiting "the spitting of pus."

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ABSTRACTS OF TUBERCULOSIS

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Progress in Tuberculosis 1932-1933.—There has been no outstanding advance in diagnosis of pulmonary tuberculosis, but both clinician and roentgenologist are realizing the importance of roentgen-ray diagnosis, especially in early cases when physical signs are not definite, and in nontuberculous pulmonary infections which may have many of the same symptoms found in pulmonary tuberculosis. Advance in treatment is due to the general acceptance of surgical measures, pneumothorax, phrenic-nerve operations and thoracoplasty.—*Progress in Tuberculosis 1932–1933, J. B. Hawes, 2nd, & M. J. Stone, New England J. M., February 1, 1934, ccx, 260*—(*R. C. S.*)

Tuberculosis in Young Women.—Since the beginning of the century, tuberculosis in the middle-aged and elderly people has steadily decreased but in young males the decrease has slowed up and in young females it has ceased altogether. In the age-group, 15 to 25 years, one-third of the deaths from all causes among males and almost half the deaths among females are due to tuberculosis. From 1911 to 1913, 1,198 girls of this age-group died of pulmonary tuberculosis while from 1920 to 1922, 1,607 died. Noting the increase, one might think the ill effects of the war were persisting, but the report of the School Medical Officer for the year 1920 states that during the war there was a notable improvement in the general physical condition of the children. One school of thought explains the increase as an alteration of the relationship of the tubercle bacillus with young people. A second suggests it as due to a larger proportion of persons reaching young adult age without previously having acquired tuberculous infection. The third group suspects modern social conditions as a factor. In this connection data were obtained from 682 single girls, age 15 to 25 years. Fifty per cent of the group were found to be clerks, domestics, dressmakers, and shop assistants. The habits and social conditions of 100 girls of this group were compared with a control group of healthy girls similarly occupied and from the same level

of society. No significant difference could

times before tuberculous infectiousness for guinea pigs was lost. Samples of udder milk

left the security and comfort of domestic. Somerset 2 contained tubercle bacilli and 20

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bercuiose infection of the intestinal canal is

may lead to pneumothorax through rupture